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Southern Medical Association, Forty-Fifth Annual Meeting, Dallas, Texas, November 5-8, 1951

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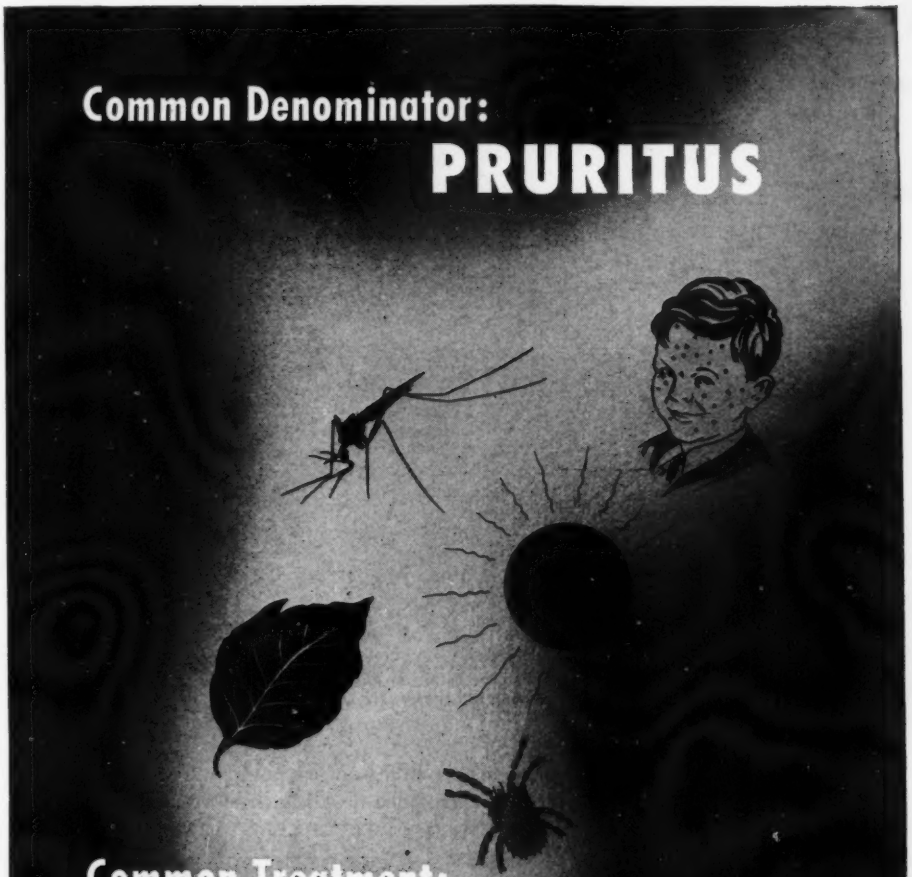

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1. Donegan, J. M., and Thomas, W. A.: Capillary Fragility and Cutaneous Lymphatic Flow in Relation to Systemic and Retinal Vascular Manifestations: Rutin Therapy, Amer. J. Ophthalmology 31:671-78 (June) 1948.

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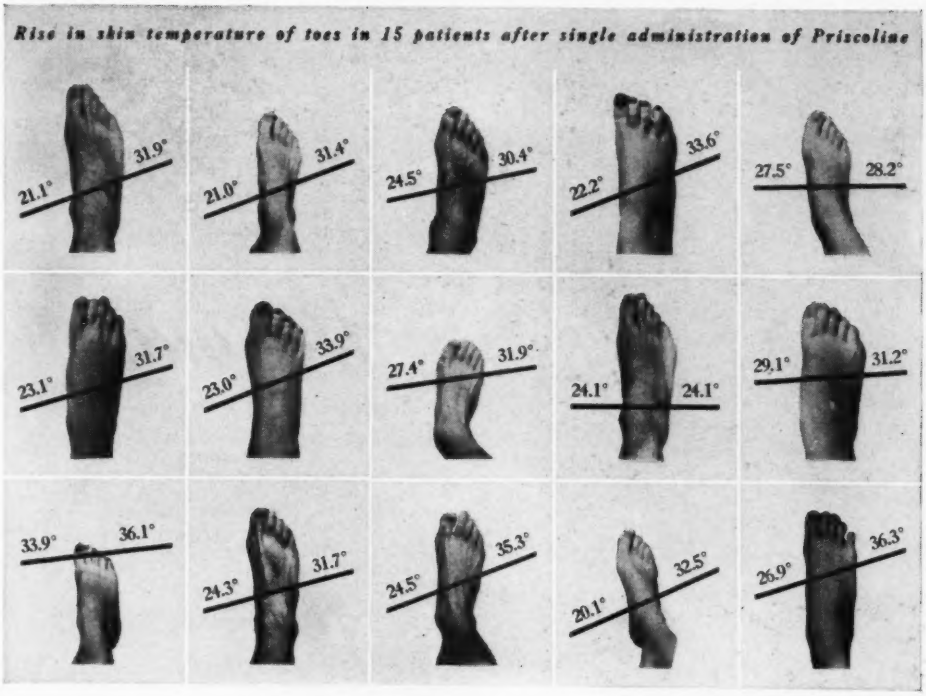

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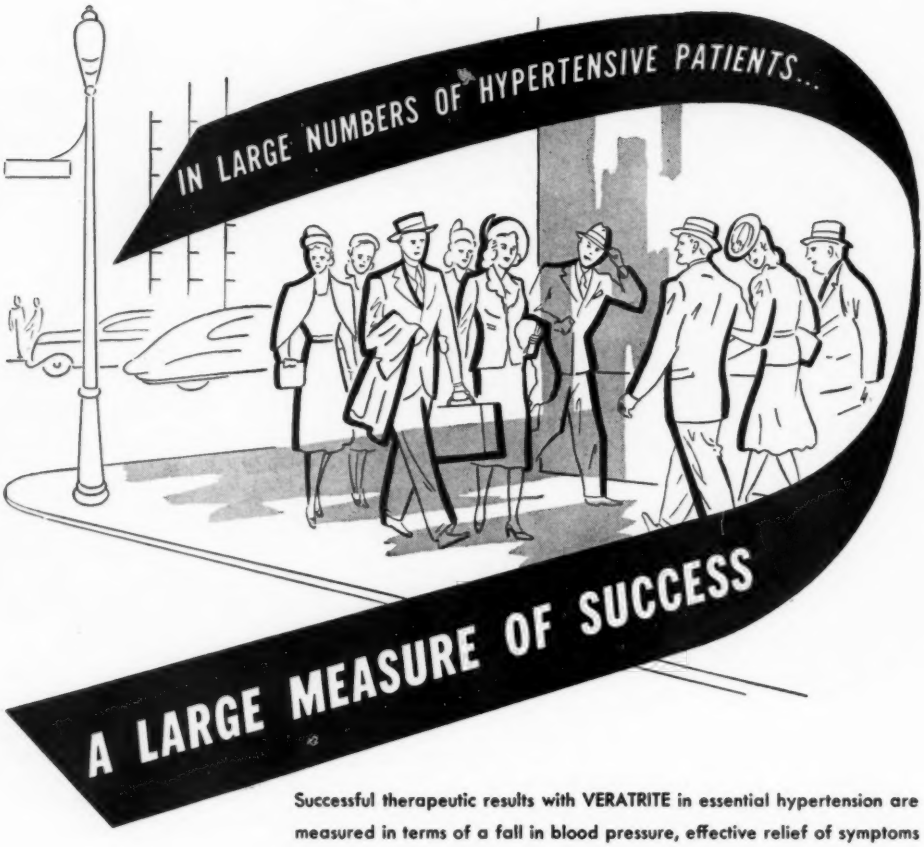

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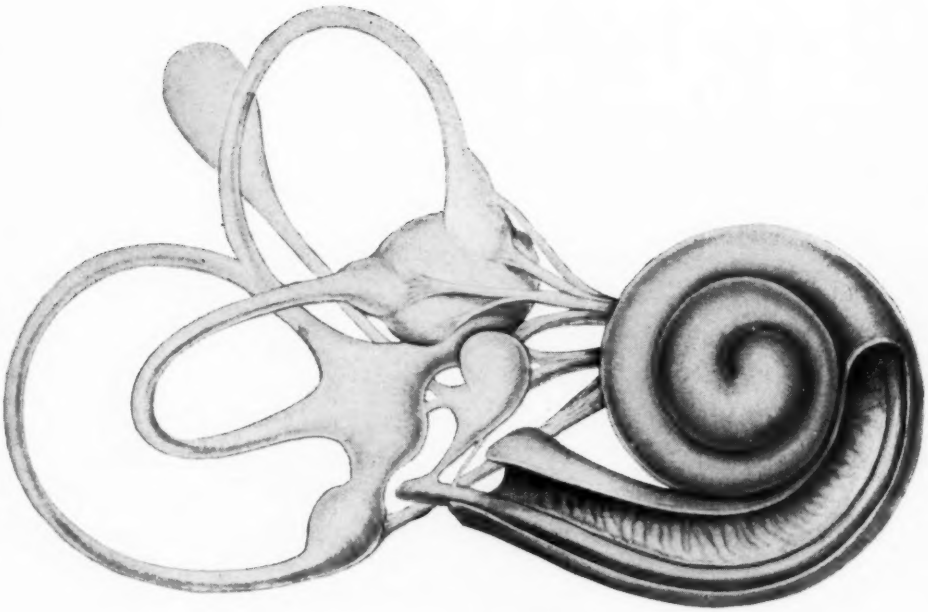

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*Eastman, N. J. & Seibels, R. E.: *The Efficacy of the Suppository and of Jelly Alone as Contraceptive Agents*, J. A. M. A. **139**:16 (Jan. 1) 1949. **Reprint on request.**

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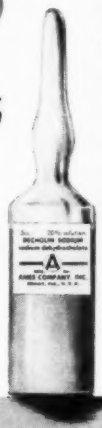

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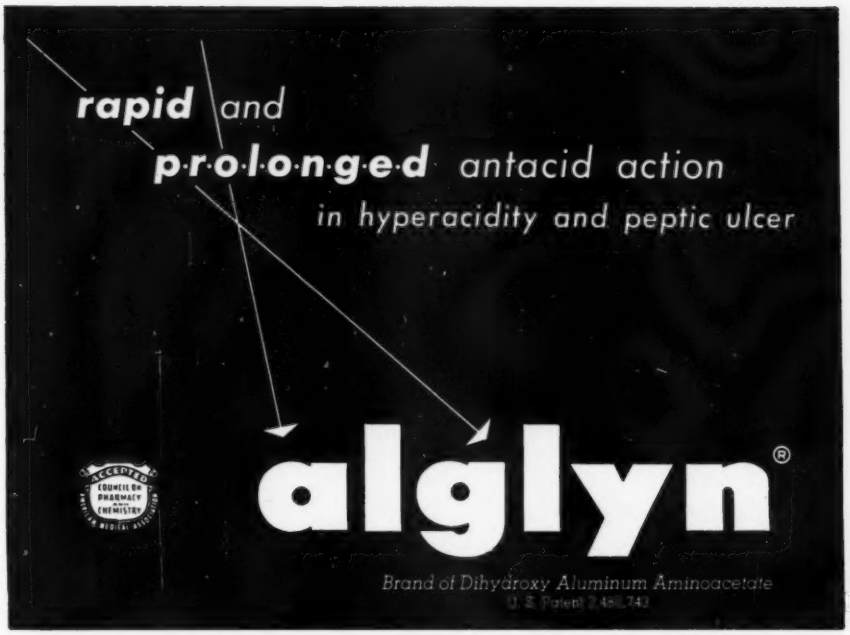

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References:

1. Hammerlund, E. Roy, and Rising, L. Wait, A Comparative Study of the Buffering Capacities of Various Commercially Available Gastric Antacids, J.A.Ph.A., Scientific Edition, 38: 586-588 (1949).
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5. Holbert, J. M., Noble, Nancy, and Grote, I. W., J.A.Ph.A., Scientific Edition, 37: 292-294 (1948).

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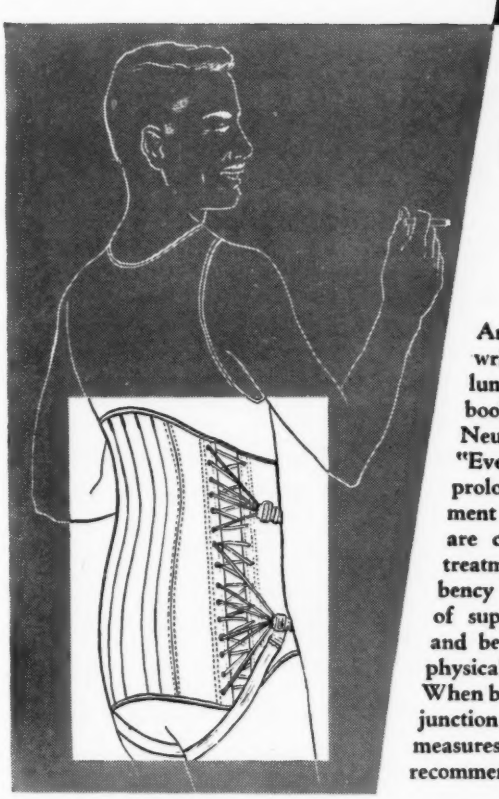

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Philip Lewin, M.D., F.A.C.S.
Backache and Sciatic Neuritis,
Chapter XXXIX, Page 580
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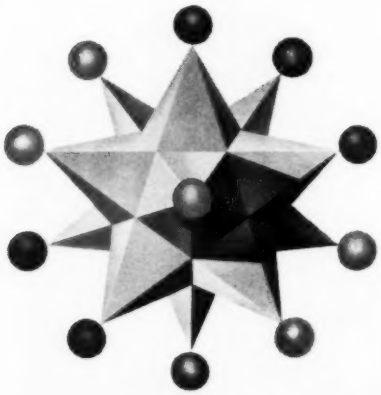

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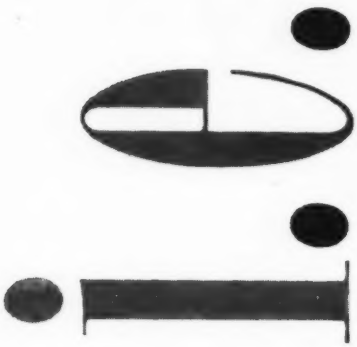

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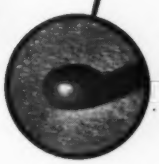

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*Wilbur, D. L.: Principles in the Use of Vitamins in Treatment: I. Vitamin Deficiency Diseases. Gastroenterology, 1:179, Feb., 1943.

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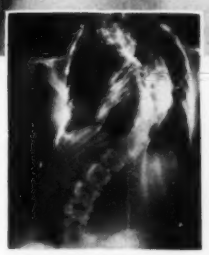

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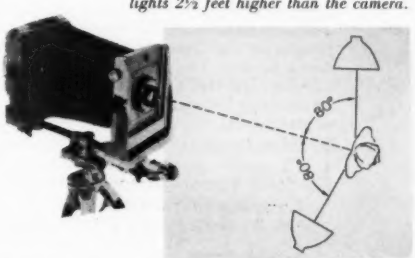

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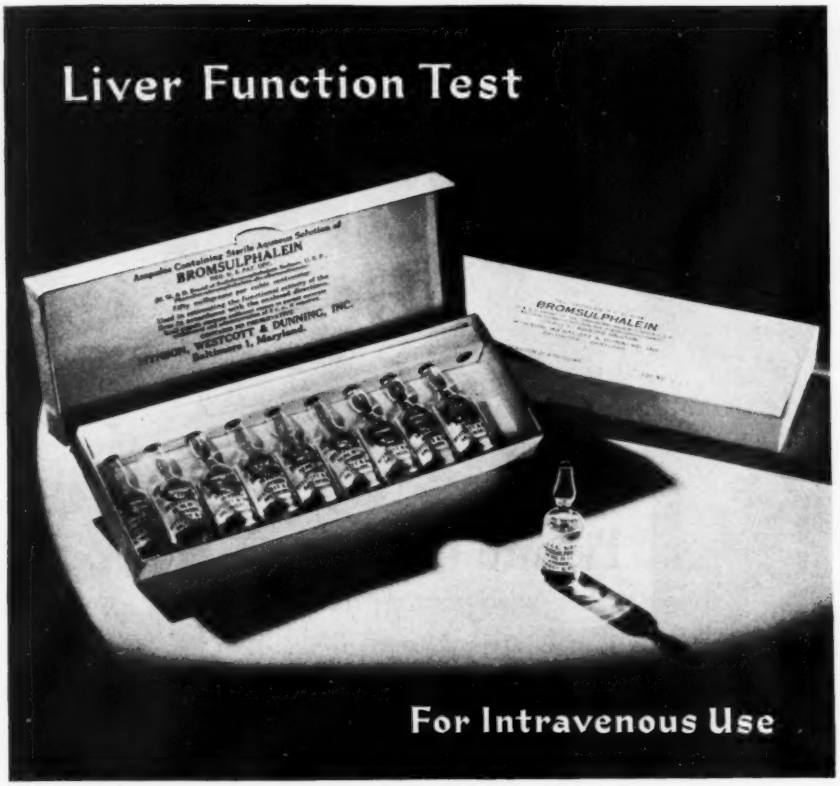

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Volume 44 JULY 1951 Number 7

CIRRHOSIS: A DYNAMIC DISEASE*

By JEROME S. LEVY, M.D.
ALFRED G. KAHN, JR., M.D.
and
ROBERT W. TALLEY, M.D.
Little Rock, Arkansas

Cirrhosis has been an especially baffling disease and its former hopeless outlook most discouraging to anyone called upon to treat such a case. This viewpoint has been the result of the concept of cirrhosis of the liver as a static disease which is expressed as a scarred parenchyma for which nothing can be done.

Rational treatment of any disease condition, however, becomes possible with the development of the proper conception of its pathologic changes. The physician must understand the mechanism by which these changes alter the function of a diseased organ and plan the management of the case to meet both the structural and functional alterations which have occurred. The more numerous the functions of a particular organ, the more difficult is the problem of its treatment when diseased. The liver presents a confusing picture because of its many functions, its great reserve, and the misunderstanding of the pathologic changes which only now are becoming understood.

Many of us were taught that the liver was the recipient of repeated insults of a toxic character which produced scarring followed by efforts at regeneration. With the repeated insults, the liver pattern was altered each time. The end result was a small, scarred, nodular organ. This concept has been changed in recent years with the progress of our knowledge of the liver.

Two developments have been largely responsible for the better understanding of cirrhosis. In a large series of cases of cirrhosis, Patek[1] demonstrated definite clinical and laboratory improvement even in advanced cases. The concept that cirrhosis was not a static disease, but that in some stages it might be reversible, began to take form. An equally important contribution was the popularization of the liver punch biopsy by Roholm and Iversen.[2] This has offered an opportunity to study liver disease in different phases of development in the same patient. It now has become evident that cirrhosis, far from having an unchanging pathologic picture, can show improvement or increased injury, and a single patient may go through many cycles. This changing, dynamic picture explains many of the discrepancies in our understanding of this disease. With this concept the physician can offer hope and the outlook of comparative health to his patient.

We have reviewed all of the cases of advanced cirrhosis at the University of Arkansas School of Medicine during the past 5 years. These cases were all on the gastro-enterological service of one of us (J. S. L.). Forty-two cases fulfilled the criteria of Laennec's cirrhosis. Of these, 24 are living and 18 are dead; out of the 18 who died 10 were autopsied, and 3 of these had also had needle biopsies. Of the 42 cases, 27 patients had needle biopsies performed, a number having had multiple ones.

Three cases have been selected from this series of cases under our observation to demonstrate the changing picture occurring in cirrhotics.

CASE REPORTS

Case 1, J. B. (84836).—This 47-year-old white woman was first admitted to the University Hospital on July 20, 1948, complaining of vague epigastric discomfort and pain present since an appendectomy and hysterectomy five years before. Two years prior to this admission she became jaundiced and developed severe anorexia, both of which subsided after two months bed rest.

*Read in Section on Gastroenterology, Southern Medical Association, Forty-Fourth Annual Meeting, St. Louis, Missouri, November 13-16, 1950.

*Department of Medicine, Division of Gastroenterology, University of Arkansas School of Medicine, Little Rock, Arkansas.

*The authors wish to express their thanks to Dr. A. Nettleship for the cooperation of the Department of Pathology.

Essential findings on physical examination were several spider angiomata, slightly tender liver palpable 6 cm. below the right costal margin, and splenomegaly.

During six weeks of observation and treatment in the hospital, the liver regressed slightly, the spleen increasing in size. Hematologic studies were constant, with a slight anemia and leukopenia and a relative lymphocytosis. Serologic tests were negative. An oral cholecystogram was reported as normal. The results of the laboratory studies and needle biopsies of the liver are shown in *Chart 1* and *Fig. 1A, B, C* and *D*.

The patient was discharged from the hospital on September 1, 1948, only to be readmitted on November 25, 1948 for additional observation. There had been an increase in all of the previous symptoms in the preceding two weeks. Her liver was palpable two inches below the right costal margin in the midclavicular line, and an extremely tender spleen was palpable at the left iliac crest. Needle biopsy was repeated (*Chart 1* and *Fig. 1E*).

After discharge from the hospital, the patient was followed in the clinic. In December, 1949, she vomited blood on one occasion. She returned last on September 22, 1950. There had been no marked change in the past year. The liver was not palpable, and the spleen was palpated 6 cm. below the left costal margin. There was no edema or ascites. The liver profile is shown in *Chart 1* and the liver biopsy findings in *Fig. 1F*.

The clinical picture in this case was that of a chronically ill woman. A diagnosis of early cirrhosis was made and confirmed by the microscopic evidence of the needle biopsies of the liver (*Chart 1* and *Fig. 1*). She has been studied by

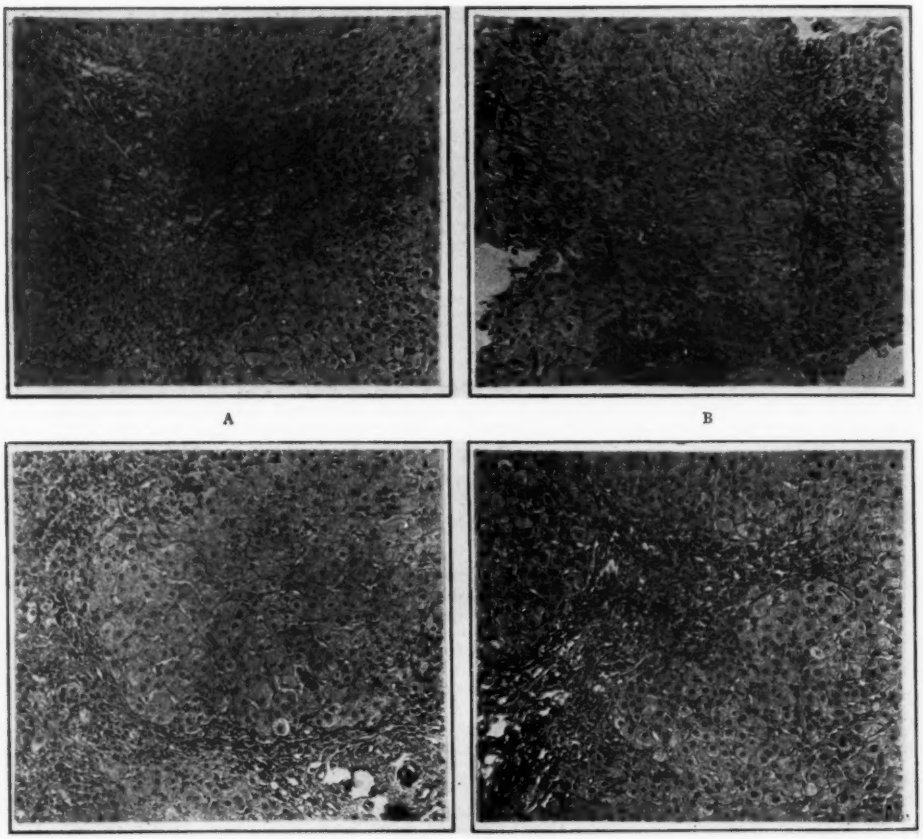


Fig. 1

(A) Needle biopsy July 20, 1948. There is an increase in the fibrosis in the portal and perilobular areas. Round cell infiltration is noted in the same areas. This extends into the liver lobules. Sinusoids are compressed.

(B) Needle biopsy August 5, 1948. There is fibroblastic proliferation in the portal areas with some round cell infiltration. The inflammatory reaction is much less than on July 20.

(C) Needle biopsy August 19, 1948. There are strands of fibrosis producing a nodular type of cirrhosis. There is an increase in round cell infiltration over that noted on August 5.

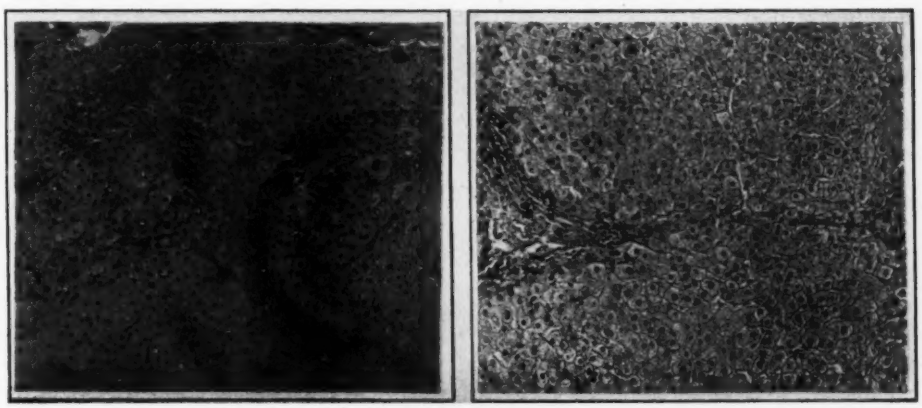
(D) Needle biopsy September 1, 1948. There is an increase in the density of the fibrous bands with some round cell infiltration. The density is greater than in the previous biopsies.

means of six liver biopsies and numerous liver function tests over a two-year period. The various laboratory tests (*Chart 1*) made during the early part of the study indicated liver damage. This was reflected in the persistently abnormal bromsulfalein retention, the last one in September, 1950 being unquestionably abnormal. The microscopic picture seen in the liver biopsies

Date	BSP	Thymol Turb. Units	Serum Bilirubin Mg. Per Cent	Serum Protein Gm. Per Cent	Alkaline Phosphatase King-Armstrong Units	Ceph. Chol. Floc.	Prothrombin Time Per Cent	Needle Biopsy
7-20-48	0 per cent 30 min.	18	0.7		4.8		109	Increased fibrosis in portal and perilobular areas with round cell infiltration which extends into lobules. Some binucleated cells. Compression of sinusoids (*Fig. 1A*)
8-5-48		2.3	1.1	7.4			100	Fibroblastic proliferation with some round cell infiltration. Liver cords looked more normal with better architecture of the lobule than on 7-20-48 (*Fig. 1B*)
8-19-48	10 per cent 30 min.	15	1.2	6.8 Alb. 3.5 Glob. 3.3	10.2			Strands of fibrosis producing a nodular type of cirrhosis. Round cell infiltration is again prominent; is found in central portion of liver lobules. There is increased fibrosis and round cell infiltration over previous biopsies (*Fig 1C*)
9-1-48	35 per cent 15 min. 10 per cent 45 min.	11			14.4		95	Bands of fibrosis which are more dense than previously. Round cell infiltration in portal and periportal areas, some deep in lobules. Fibrous bands are more extensive and wider (*Fig. 1D*)
11-25-48	10 per cent 15 min. 5 per cent 45 min.	6.0		6.80 Alb. 3.99 Glob. 2.81			89	Portal fibrosis present but bands are narrower; some round cell infiltration. Definite improvement noted on comparison with appearance 9-1-48 (*Fig. 1E*)
9-22-50	63 per cent 15 min. 16 per cent 45 min.	9.9	0.5	6.72 Alb. 3.94 Glob. 2.78		3+ — 24 hrs. 4+ — 48 hrs.		Section appeared essentially normal with a minimum of portal fibrosis (*Fig. 1F*)

Chart 1

LABORATORY FINDINGS IN *CASE 1*



E F

Fig. 1 (continued)

(E) Needle biopsy November 25, 1948. The fibrous bands are sharply defined, compressed, and dense. The cellular reaction is less than in the previous biopsies.

(F) Needle biopsy September 22, 1950. The fibrous tissue is very inconspicuous. Fine strands of fibrous tissue are seen throughout the section. The portal areas are not notably thickened. No cellular reaction was noted.

showed a constantly changing inflammatory reaction which improved, regressed, and improved again. Comparison of the series of biopsies showed differences in the extent of the fibrosis in the area from which the specimens were obtained. The laboratory tests taken at the end of the two years of study reflect a greater liver damage than was shown in the essentially normal microscopic sections.

It was especially interesting to us to note the changes in the microscopic picture during the course of this patient's disease. The cellular infiltration of the portal and perilobular areas and in the lobules was quite variable and fluctuated from marked to practically none as noted in the last biopsy. This was not unexpected, as this type of reaction is expected to vary with changing degrees of activity of the inflammatory process. However, the changes in the density and extent of the fibrous reaction were surprising and unexpected although a similar observation was reported before this section in 1948.[3] There was a definite difference in the fibrosis noted in July and in November, 1948, the bands being narrower and smaller in the latter with the lobules and the cells in the lobules more normal in appearance. The picture two years later (September, 1950) was even better, there being very little fibrosis and only one area of cellular accumulation.

Several reasons may be advanced to explain these findings. The degree of cellular reaction may cause the portal areas to appear larger and more extensive than they actually are, and the disappearance of the cellular infiltration permits restoration of the normal width and amount of the fibrous tissue present. However, with less cellular reaction seen in the second and third biopsies of August, 1948, there was no detectable change in the fibrous bands. The amount of fibrosis noted in the biopsy taken in September, 1950, was so minimal that it is difficult to believe the sections are from the same liver. A second explanation suggests that there is contraction of scar tissue with apparent reduction in extent. The findings in this case would suggest an extreme amount of contraction, but there was not an associated distortion of the liver lobules noted in the sections such as would be anticipated if this were the sole explanation. In a previous report before this Association by one of us (J. S. L.),[3] a series of slides were shown which suggested that there may be regression of scar tissue in the liver. This may be so in this case, though we do not know what mechanism produces it. The recovery of the hepatic cells and the restoration of the lobule to normal may compress the portal areas and be an additional explanation of the findings in this case and the one previously reported. Another possibility is that the disease process in the liver is not uniform throughout the organ. A recent report by Waldstein and Szanto[4] implies a 10 per cent error in the findings when the liver is examined by taking a number of punch biopsies in scattered areas of the liver. However, the first five biopsies taken in this patient were all within an inch radius below the costal margin near the midline. It would be expected that the process would be rather uniform in this limited area at any rate. The last biopsy was taken through the eighth intercostal space in the mid-axillary line. Its location in a different area of the liver may be an explanation of its difference in fibrosis. Whatever the explanation, there have been definite changes in the liver with marked improvement in the microscopic picture observed over a two-year period of time.

Case 2, G. M. (94320).—This 19-year-old Negro woman was admitted to the University Hospital on November 27, 1948, with a history of constant severe epigastric pain, nausea, and vomiting of one week's duration. Three days before admission she noted dark red urine. In June, 1948, she had received antisyphilitic therapy (penicillin) at another institution. Physical examination revealed a slightly tender liver palpable 6 cm. below the right costal margin. A six weeks hospital course was afebrile. She developed jaundice two days after admission; this disappeared in 3 weeks. By December 21, 1948, her liver decreased in size, but was described as feeling nodular and granular. At discharge from the hospital on January 6, 1949, her symptoms had disappeared, but the liver was still palpable 3 cm. below the costal margin. The laboratory data are shown in *Chart 2*.

The urine urobilinogen was positive 1:20 on three occasions. Two needle biopsies were done (*Fig. 2*).

The patient was free of symptoms until May, 1950, when she developed weakness and anorexia. At that time the liver was palpable 2 cm. below the right costal margin and was not tender. She refused another biopsy.

The etiologic factors in this case are not clearly defined. Homologous serum hepatitis, introduced during the antisyphilitic therapy, is suggested as a cause of the stimulation of fibroblastic proliferation noted in the second needle biopsy. We suspect the acute hepatitis occurred in an already cirrhotic liver, possibly luetic in origin. Only two biopsies were obtained on her, but the appearance of the two taken only three weeks apart reveal

the rapidity with which the pathologic condition in the liver can change. It is regretted that we have been unable to follow this patient more thoroughly. Her definite clinical improvement was parallelled by that noted in the needle biopsy specimen. Even in the face of additional insults, as in this case, the liver can improve with a favorable outlook for the patient.

Case 3, J. W. (14079).—This 55-year-old white man was admitted to the hospital on September 21, 1947, with a history of intermittent alcoholism. For 6 days prior to admission he had been drinking heavily. During the 6 hours before hospitalization he had severe nausea and violent vomiting. This precipitated his admission. The most remarkable physical finding was a liver enlarged to 4 finger breadths below the right costal margin.

Under therapy, his clinical improvement began almost immediately and continued until his discharge on October 9, 1947. The laboratory findings and needle biopsies are shown in *Chart 3* and *Fig. 3*.

This case represents portal cirrhosis with marked fatty metamorphosis due to chronic alcoholism or dietary insufficiency. Under treatment marked improvement in the fatty metamorphosis is demonstrated by two successive liver biopsies. The fibrous reaction is essentially unchanged. Clinically, the patient was markedly improved and improvement was demonstrated in the liver function tests. We have noted a dissimilarity between the laboratory tests and the microscopic picture in the presence of alcoholism. Extensive fatty changes may be present without any influence on the cephalin cholesterol flocculation and thymol turbidity in some cases, yet with marked effect in others. The second biopsy showed definite improvement in the hepatic cells with no change in the fibrosis. There was an absence of cellular reaction.

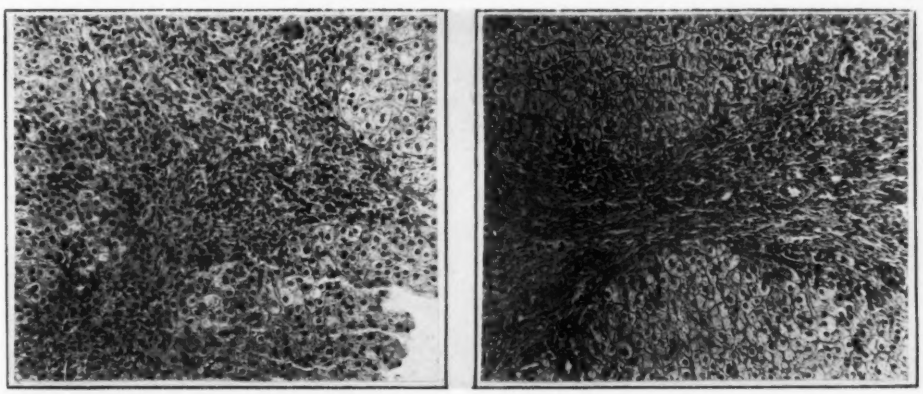
DISCUSSION

A diagnosis of cirrhosis was made in this series on the basis of the clinical picture, the pathologic evidence and laboratory findings. It is our feel-

Date	BSP	Thymol Turb. Units	Serum Bilirubin Mg. Per Cent	Serum Protein Gm. Per Cent	Alkaline Phosphatase King-Armstrong Units	Ceph. Chol. Floc.	Prothrombin Time	Needle Biopsy
12-17-48		10	0.7	8.0 Alb. 4.1 Glob. 3.9	34.2		98	Fibroblastic changes in periportal and perilobular areas with occasional broad areas of round cell infiltration. Some bile staining of hepatic cells present (*Fig. 2A*)
1-6-49	24 per cent 15 min. 0 per cent 45 min.	10.5		7.6 Alb. 4.4 Glob. 3.2	68.8	neg.		Fibrosis in portal and perilobular areas; sharply defined with fibroblastic proliferation and very slight round cell infiltration (*Fig. 2B*)

Chart 2

LABORATORY FINDINGS IN *CASE 2*



A B

Fig. 2

(A) There are fibroblastic changes in the periportal and perilobular areas with an occasional broad area of round cell infiltration. There was some bile staining of the hepatic cells.

(B) The fibrosis in the portal and perilobular areas is sharply defined and rather dense. Very slight round cell infiltration remains.

ing that the liver biopsy afforded the best criteria.

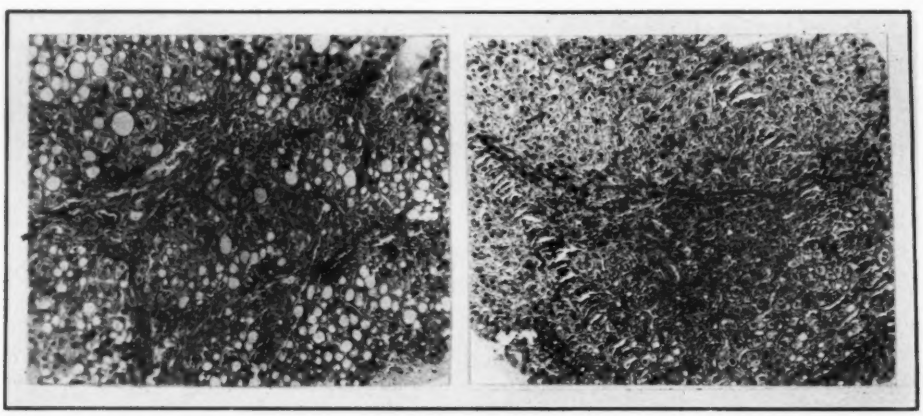
From a pathologic point of view, improvement in the appearance of the parenchymal cells often can be readily demonstrated. The clinical improvement noted in cirrhotics under treatment is probably due to the improvement in the parenchymal cells. There is great doubt of the possibility of decrease in the abnormal fibrosis. The findings in *Case 1* and in the previously reported case suggest this is possible. Ricketts, Lushbough, Kirsner and Palmer[5] deny decreases in fibrosis.

Our former knowledge of the pathologic changes in the liver was based upon autopsy findings, with an occasional surgical biopsy section added to the collection. Cirrhosis was seen in the terminal stages. The picture was essentially the same in each case, and, therefore, our understanding of the process was rather rigidly fixed on scarring, distortion of the liver lobule, attempts at regeneration of the hepatic cells and finally a squeezing out of liver function by the extensive scarring. It is now possible to follow the development of these changes over a long period of time. It is admitted that the microscope cannot determine functional activity but even within the limits of the suspected error of sampling an extensively damaged liver can be observed going through a period of recovery. In some cases the process is progressive and recovery does not occur. The sections in *Case 1* demonstrated the constantly changing picture of acute and subacute inflammatory reaction in the liver and the improvements and reactivation which can and do occur. There is suggested, too, that the fibrosis may become altered with definite improvement as seen in the microscopic sections. This has been seen previously in another case.[3]

Date	BSP	Serum Bilirubin Mg. Per Cent	Serum Protein Gm. Per Cent	Ceph. Chol. Floc.	Prothrombin Time Per Cent	Needle Biopsy
9-22-47	20 per cent 45 min.		8 Alb. 4.2 Glob. 3.8	neg.	57	Marked portal fibrosis with distention of the cord architecture. Fatty degeneration of the hepatic cells is extensive; very few normal cells could be identified with entire slide (*Fig. 3A*)
10-9-47	0 per cent 15 min. 0 per cent 45 min.	2.1	6.4 Alb. 3.2 Glob. 3.2	neg.	73	Portal fibrosis with narrow bands setting off small discrete lobules without central veins. Some fatty degeneration is noted in the hepatic cells, but much less than 17 days before. Cell regeneration within hepatic cords (*Fig. 3B*)

Chart 3

LABORATORY FINDINGS IN *CASE 3*



A B

Fig. 3

(A) There is marked portal fibrosis with distortion of the cord architecture. There is extensive fatty degeneration of the hepatic cells, very few normal looking ones being seen in the entire slide.

(B) There is portal fibrosis present producing small, discrete lobules without central veins. These are set off by narrow bands of fibrosis. Although still present to a noticeable degree, the fatty degeneration noted 17 days before is markedly less and cell regeneration is noted.

Sellers[6] has observed it experimentally. The mechanism by which this occurs is not known. We do not know whether this is more apparent than real but we have observed it in two cases which we were able to follow over a long period of time and offer this provocative idea to stimulate others to search for it and thus further our understanding of cirrhosis.

The three cases presented serve to emphasize the fact that the liver has remarkable powers of regeneration and healing, and that the cirrhotic liver is one in which demonstrable changes may be constantly occurring. An early diagnosis of cirrhosis of the liver is as important in the prognosis as is the early diagnosis of malignant disease. The proper management may be effective in controlling the extent of the disease and possibly may effect a regression of the changes in the liver. Further studies are indicated to establish the point at which the processes are still reversible. The liver biopsy is a definite aid in following the course and in predicting the prognosis in cases of cirrhosis of the liver. We believe that there is definite correlation between the clinical course and the pattern of the disease as shown in the histological pattern of the liver biopsy. The liver function tests are considered to be helpful, but frequently are difficult to correlate with the clinical course and the liver biopsy in our experience.

CONCLUSION

(1) Cirrhosis of the liver is a dynamic disease showing a constantly changing picture of injury and recovery. The stage at which the changes become irreversible has not been demonstrated.

(2) Punch biopsy makes possible careful observation of the course of a disease process in the liver.

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Discussion follows next paper, page 579.

A CRITICAL EVALUATION OF THERAPY IN CIRRHOSIS OF THE LIVER*

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Since the initial publication of Patek and Post,[1] which stimulated new interest in the management of cirrhosis of the liver, numerous modifications of treatment have been suggested. Most of these have been reasonably successful, and except for a few workers, optimism regarding treatment of this disease has prevailed. In an attempt to evaluate some of the therapeutic modifications which have been suggested a study of the results of treatment in 84 patients with cirrhosis was undertaken. For convenience of discussion they have been divided into 3 groups: group 1, 29 patients with early stages of cirrhosis; group 2, 39 patients with advanced stages of the disease; and group 3, 16 patients who succumbed. Of the 68 patients still living, 46 have been followed one year or longer, 29 two years or more and 14 three years or more.

This series differs from the usual reported series only in that a relatively large number of patients were seen in the early stages of the disease. The reason for this is that needle biopsy of the liver is done routinely on all patients suspected of having hepatic disease who come to the clinic.[2] In addition to a searching history, thorough physical examination and the usual laboratory procedures, special hepatic investigations performed in each case included bromsulfalein retention test, serum bilirubin determinations, cephalin flocculation test, serum protein determination with albumin-globulin ratio, two-hour urine urobilinogen excretion test and prothrombin time estimation.[3] The basic therapeutic regimen consisted of a diet of 500 grams of carbohydrate, 200 grams of protein and sufficient fat to render the food appetizing,† moderate vitamin supplements,‡ and brewer's yeast, ½ ounce three times daily. Variables included use of a low caloric diet (1,500 calories or less) with 150 gram pro-

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†Usually 150 grams making a total caloric intake of 4,150.

‡One Squibb therapeutic capsule daily.

tein, methionine* 1 gram four times daily and intravenous injections of liver extract.

In 29 patients with cirrhosis in the early stages (*Group 1*) results have been uniformly good. Most of these patients were asymptomatic when seen and had only mild to moderate hepatomegaly. Bromsulfalein excretion was the only laboratory test which gave a consistently abnormal result, though it was usually less than 20 per cent retention at 45 minutes after injection of 5 mg. per kilogram of body weight. Histologic sections of the liver revealed fatty infiltration of varying degree, mild hepatocellular damage and moderate chronic inflammation. That these lesions represented early cirrhosis has been substantiated by demonstration of progression to well developed cirrhosis in untreated or uncooperative patients. The only patients in this group who failed to improve were 2 alcoholic persons who continued their usual alcoholic and dietary habits for the first year of treatment, but they have since reformed and are now showing steady improvement. Restriction of caloric intake in 15 of the 29 patients in this group did not affect their progress. Use of methionine in 2 patients resulted in no additional benefit. Histologically, the lesions have all regressed, in some instances completely. Clinical improvement has been uniform and unrelated to the type of pathologic change initially present. Results of laboratory studies have in most instances returned to normal.

Thirty-nine of the 84 patients were severely ill when first seen (*Group 2*). Superficial inspection revealed unmistakable signs of hepatic disease and the results of laboratory tests were definitely abnormal. The majority were jaundiced or manifested disturbances of serum proteins and 12 of these 39 patients had ascites. Of the 27 without ascites initially, 12 exhibited pronounced improvement clinically, in the results of the laboratory tests, and histologically. In 11 of these considerable fatty change in the liver as well as increased fibrosis and inflammation was noted pathologically when first seen as contrasted with *Group 1*. Twelve of the remaining 15 made favorable clinical progress but improvement in the results of their laboratory tests was less dramatic than that in *Group 1*. Those patients with relatively inactive fibrosis usually improved in nutrition, as exhibited by favorable changes in results of prothrombin estimation and serum protein determinations, but showed little change in ability to excrete bromsulfalein. Of the 3 patients who failed to improve 2 were alcoholic patients who continued to indulge and steadily deteriorated. The other represents an example of chronic smouldering hepatitis which has changed little under observation during a period of ten months.

In the 12 members of *Group 2* with ascites, 5 had fatty livers demonstrated by biopsy and treatment resulted in immediate improvement in all 5. Two have been clinically well and working for two years or more and one for more than a year. The 3 with inactive lesions histologically have not improved. The other 4 who had considerable inflammation and necrosis without fat have improved only slowly but when last seen had no ascites. Of the entire group, 6 were on restricted caloric intake and 11 were given additional methionine without significantly influencing their progress.

Of the 16 patients who are now dead (*Group 3*), 5 died of causes unrelated to the hepatic disease. Nine of the other 11 had advanced cirrhosis initially without any fatty infiltration in the liver and their course was steadily downhill to death. One patient, an uncooperative alcoholic with a fatty liver, responded to therapy in the hospital but discontinued the treatment when discharged. One patient died of hemorrhage but autopsy failed to disclose whether this resulted from paracentesis or liver biopsy. As in the other groups, use of methionine seemed to make little difference in the progress of these patients.

Intravenous injections of crude liver extract in dosage of 10 to 20 cc. daily were administered to 8 of the patients with ascites and little or no fat in the liver. Only 4 showed any improvement. This preparation appeared to help by promoting both appetite and diuresis but in view of the small number thus treated, this is only a clinical impression.

DISCUSSION

An evaluation of results of treatment of cirrhosis of the liver is not significant unless the diagnosis has been incontrovertibly established by histologic demonstration of the lesion. This has been done in each case in this series. Moreover, as many variables as possible must be elimi-

*Courtesy of Dr. E. F. Roberts, Division of Research, Wyeth, Inc., Philadelphia, Pennsylvania.

nated. Gallstones particularly may be associated with recurrent cholangitis and result in continuous damage to the liver. In such cases not only is cholecystectomy necessary but it must be done as soon as safety permits. It has been done in 5 instances in this series and should have been done in 2 additional patients who died. Fatal hemorrhage from esophageal varices is an ever present possibility. Patients with known varices and previous bleeding have been eliminated from this study except in cases in which surgical correction was possible. Good results in the present series may be attributed to such selection, to the relatively large number of patients with early stages of the disease, and to cooperation of the patients in following instructions closely.

Although methionine has not been found to be of value in routine treatment of cirrhosis, in individual instances in which food intake in the early period of treatment presented a great problem, methionine alone exerted a definite lipotrophic effect and apparently was of value in initiating improvement. Of particular interest are the patients in each group in whom the results of liver function tests returned to absolutely normal values. Such instances, in which follow-up studies of as long as five years show complete arrest of the morphologic changes in the liver and a single patient who died of coronary occlusion four years after initial study and in whom necropsy showed absolutely no progress of the hepatic lesion, present strong evidence against the conception that cirrhosis is a necessarily progressive disease.

CONCLUSIONS

(1) Many patients with early stages of cirrhosis of the liver can be cured.

(2) In most patients with advancing cirrhosis the disease can be stabilized and the patients can lead a useful life if they will help themselves.

(3) Except in special instances a diet which provides 150 grams protein daily with modest vitamin supplements is sufficient.

(4) Methionine is of value in patients with severe cirrhosis and fatty liver who do not eat well.

(5) Intravenous injection of crude liver extract is probably of adjuvant value in the management of advanced cirrhosis with recurrent ascites.

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DISCUSSION (*Abstract*)

Discussion on papers by Drs. Jerome S. Levy, Alfred G. Kahn, Jr., and Robert W. Talley, and Dr. W. D. Davis.

Dr. John Tilden Howard, Baltimore, Md.—Having been able to follow eighty-odd cases of hepatic cirrhosis, Dr. Davis is in a much better position than I am to evaluate the modern therapy of the disease. But from continuing clinical observation of a small group of patients with cirrhosis, by estimation certainly no more than a dozen, I can agree with his finding that nutritional treatment is most successful in early cirrhosis and that the outlook for patients with advanced forms of the condition, particularly when fatty infiltration is absent, is still pretty grim. Of Dr. Levy's 42 cases, 24 are living and 18 are dead.

Perhaps I overlook mild cirrhotics in my practice and that may be the reason for the approximate dozen cases of hardened livers which I have had under observation. I noted that 29 of Dr. Davis' cases were only slightly or moderately ill and, though his paper dealt with the treatment of hepatic cirrhosis, I wish to inquire concerning his criteria for the clinical diagnosis of the disease. It is possible that I overlook cases which others might treat. My clinical diagnosis of hepatic cirrhosis does not require symptoms of the condition, though I find them to be present usually. The diagnosis does require hepatic enlargement, which is real and not the result of ptosis, and two or more abnormal tests of hepatic function.

In July of 1949 a man 61 years of age, who had previously been in good general health and who had taken alcohol only occasionally, had an attack of severe vertigo with vomiting. His physician found no obvious cause for the attack and an otolaryngologist made the diagnosis of acute labyrinthitis. But this patient was not satisfied by the simple tagging with a name of his vertigo. He demanded that a search be made for trouble behind any "labyrinthitis" which may have been present. He had the means to pay for what is called "a complete examination" and he meant to have it. Accordingly, his physician sent him to a prominent consultant in his city and his studies consisted principally of laboratory tests. There was a retention of 24 per cent of a five-milligram per kilo dose of bromsulfalein thirty minutes after its intravenous administration. Blood chemical tests were said to be normal. The patient's basal metabolic rate was reported to be minus 28 per cent. Extensive roentgen examinations were negative. The consulting internist told the patient that he had hardening of the liver in an early stage and that that had caused the dizziness.

I took it from the program which was given the patient that his liver was treated actively. He was given a high protein and high vitamin diet. Two ten-grain tablets of choline dihydrogen citrate were taken before

meals. One hundred milligrams of ascorbic acid were given after meals. And thirty intramuscular injections of liver were given between July and October of 1949. Then the patient was in a motor accident and treatment was discontinued and was not resumed.

In mid-March of this year the patient came to me for a routine annual checkup. He said that there had been no more vertigo. A few dilated capillaries could be seen on the skin of his face but there were no spider angiomata. At neither of two examinations of the abdomen was the liver enlarged. Certainly the bromsulfalein test of hepatic function was abnormal, for 32 per cent of the dye remained in the serum a half hour after the injection of 5 mg. per kilo. The cephalin flocculation test was negative. The reading of the thymol turbidity test was 2.1 units, the cholesterol was 408, the serum albumin was 5.1 and the globulin was 2.4. Incidentally, the basal metabolic rate was minus 12 per cent.

It was learned toward the end of this patient's examinations that he had had painless jaundice for a period of two or three weeks when he was in his twenties.

Perhaps a needle biopsy of the liver was indicated in this patient, but it was not done. There was no very good reason for withholding that procedure in this case except our general reluctance to employ the needle when patients are not really ill with hepatic disease, and then, I confess, needling is done less on private patients than on those in the wards. And I know of no physician who has subjected himself to the procedure when it has been advised.

But did this subjectively well man of 61 have cirrhosis? He may have had hepatic damage, I admit, yet I hesitated to dignify it by the term cirrhosis without symptoms referable to the liver, without hepatic enlargement, and without more laboratory evidence of hepatic damage than the bromsulfalein test.

The bromsulfalein test is a rather delicate one and there is evidence that the liver's handling of that dye may depend, to a large extent, on the hepatic circulation. Dr. Mateer and his co-workers found the test to be positive in 33 per cent of histologically normal livers. Dr. Davis relies on the bromsulfalein retention much more than I do.

His casually done needle biopsies do seem to support his diagnoses and perhaps we should perform them more often. I have been much impressed by his findings. Let us remember, however, that microscopic periportal cirrhosis has been found frequently in biopsies of grossly normal livers with normal functional tests; and the microscopic structure of the liver alone is not absolutely diagnostic of early cirrhosis (Mateer). It seems to me that the whole picture must be considered, biopsy, functional tests, physical findings, and history.

Dr. Levy has proved nicely the clinical observation that patients with cirrhotic livers have remissions and exacerbations. Cirrhosis develops when there are repeated episodes of trauma or of deficiency followed by destruction of hepatic cells, fibrosis and, most important, regeneration.

A NEW TECHNIC FOR TRANSVESICAL SURGERY*

By Jo C. Alexander, M.D.
Karl B. King, M.D.
and
Foster Fuqua, M.D.
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In June of 1949, one of us heard Professor Th. Hryntschak of Vienna describe his technic for doing suprapubic prostatectomy. We also saw him perform the operation and saw many of his postoperative patients in his clinic. We thought that his technic would have been published by this time. We have had good success with his method of opening and closing the bladder for transvesical surgery, which we believe justifies our bringing it to your attention before his paper has appeared in the literature.

His method of opening and closing the bladder can be used for suprapubic prostatectomy, bladder calculi, diverticulectomy, bladder tumors, or any condition in which it is necessary to open the bladder.

The bladder is exposed in the usual manner. It is then distended with fluid and an area of about 6 to 7 cm. in diameter is freed of all prevesical fascia. A gallbladder trochar is introduced into the center of the exposed area; after the fluid has been aspirated, a thumb forcep is introduced into the trochar opening in the bladder. The blades are gently spread, stretching the muscle fibers until the opening is large enough to accommodate the operator's two index fingers (*Fig. 1*). The opening is further enlarged until it is of the desired size. After completing the transvesical surgery, a purse-string suture, using No. 1 chromic gut, is introduced about 5 mm. from the margin of the opening. This is then drawn tight while an assistant invaginates the bladder musculature. A few interrupted sutures may then be added as reinforcing sutures or a second purse-string may be placed for reinforcing purposes. This gives an absolutely water-tight closure.

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*Read in the Section on Urology, Southern Medical Association, Forty-Fourth Annual Meeting, St. Louis, Missouri, November 13-16, 1950.

*From Department of Urology, Southwestern Medical School of the University of Texas, and Baylor Hospital, Dallas, Texas.

When performing suprapubic prostatectomy we have preferred to control the hemorrhage by ligating the arterial bleeding with suture ligature of triple O chromic and by further use of a Foley bag around which are sometimes placed one or two pieces of oxidized cellulose. Following this, a small forcep is used to pierce the bladder wall about 3 cm. above the original opening in the bladder, and a 22 or 24 F. whistle-tip catheter is pulled into the bladder and used as a suprapubic drain for a period of 24 to 48 hours (*Fig. 2*). This acts as a safety valve; the snug fitting catheter prevents leakage, and upon removal the muscles of the bladder, which have been separated (not cut), seem to prevent leakage. We have had suprapubic drainage of urine in only one case, and this was minimal and was of short duration. On several occasions we have removed the urethral catheter after 24 hours; and when the suprapubic tube was removed on the sixth postoperative day, there was not enough suprapubic drainage to require extra dressing. This method of suprapubic drainage was described to us by Cone and Hooks of Galveston, who say that they have used it successfully for some time.

We have been impressed by the smooth convalescence of the individuals who have been operated upon by this method, all of whom have been out of bed the next day. Many of them have left the hospital one week after prostatectomy. Until now, we have found nothing about the procedure that presents any problem to one with reasonable experience in open prostatic surgery, and for sizable glands, 60 grams and over, we feel that this technic has less morbidity than any method of prostatectomy in our experience, while functional results have left nothing to be desired.

During the past few months, we have utilized the above technic in 17 patients, of which one case was a bladder calculus, two cases were diverticulectomy of urinary bladder, and the remaining 13 were suprapubic prostatectomies. The only case which had any suprapubic drainage of urine

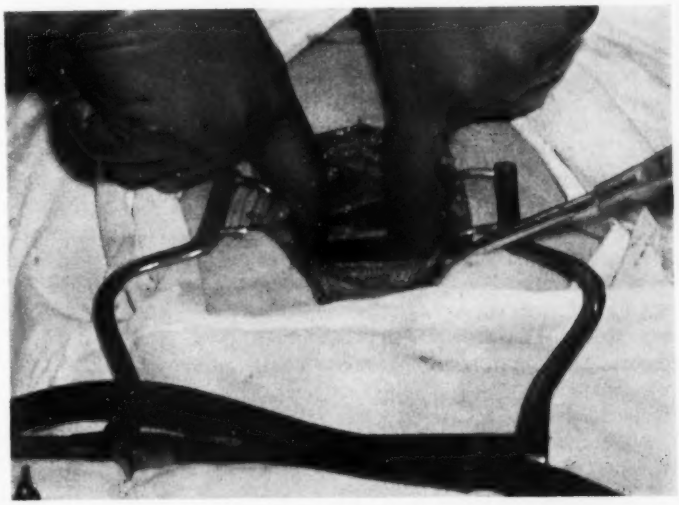

Fig. 1
Enlarging trochar opening in bladder by stretching with fingers.

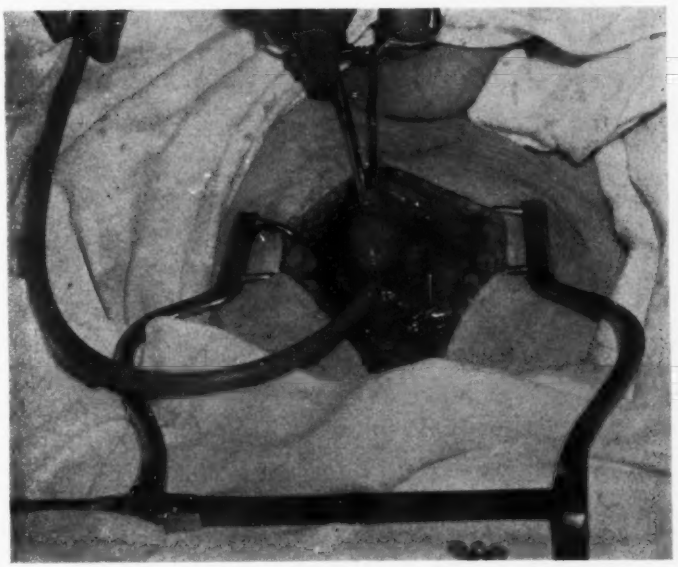

Fig. 2
Forceps separating muscle fibers 3 cm. above bladder opening for suprapubic drainage tube.

was one of the prostatectomies. This leakage was very minimal and the patient left the hospital on the eleventh postoperative day without further suprapubic drainage of urine. Following suprapubic prostatectomy, in the majority of patients the suprapubic catheter has been removed on the second or third postoperative day; and the urethral catheter on the sixth or seventh postoperative day. On three occasions the urethral catheter was removed on the second or third postoperative day, and the suprapubic tube remained in place until the fifth or sixth postoperative day. The prostatectomy cases have all been discharged with an average postoperative hospital stay of 9.9 days.

SUMMARY

We have presented our experience with Professor Th. Hryntschak's method of opening and closing the urinary bladder in 17 cases of transvesical surgery. The procedure is simple, anatomical, and in our opinion has sound surgical principles. We recommend it wholeheartedly to anyone doing transvesical surgery. The technic of introduction of a suprapubic catheter, as recommended by Cone and Hooks, will appeal to those surgeons who are still not bold enough to omit suprapubic drainage.

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426 Medical Arts Building

DISCUSSION (*Abstract*)

Dr. E. Halsell Fite, Muskogee, Okla.—This seems to be a very logical and anatomical method of opening the bladder, leaving a residual very strong one point scar, whereas, the usual incision method leaves a weaker linear scar in the bladder wall. Since reading this paper I have tried the method on a case in which I removed several large vesical calculi and obtained an excellent result without leakage. As I was going to do a vesical neck resection afterwards I also drained the bladder according to the method of Cone and Hooks as recommended in the paper and after the resection, on removal of the suprapubic catheter, I obtained immediate closure of the wound.

I should like to speculate upon what happens in this operation. Dr. Elmer Belt was showing how he stretched the anal sphincter muscle in his operation for perineal prostatectomy. Also that in a very short time, four to six days, that muscle contracts back down and becomes normal. In Dr. Hryntschak's operation a nipple of stretched muscle is turned in and a closure made over the top of it which makes it temporarily watertight. By the time the suture gives way, theoretically, the muscle has come back down to normal and the wound is completely healed, and therefore good results are obtained.

RADIOGRAPHIC FINDINGS IN PROTRUDED CERVICAL DISCS*

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and

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This study consists of the correlation of the roentgen and surgical findings in eighteen consecutive patients operated upon for protruded cervical discs at the Scott and White Clinic from 1946 to 1949.

Of the entire group of eighteen patients with the syndrome of root irritation from herniation of a cervical disc only four had entirely normal cervical spines by the usual x-ray examination. Fourteen patients showed minimal to pronounced changes in disturbance of the normal cervical curve, disturbance in the width of an interspace, proliferation of osteophytic processes from vertebral margins, or combinations of all three. Twelve of the fourteen patients with abnormality showed disturbances in the cervical curve ranging all the way from mere straightening of the lower half of the cervical spine (*Fig. 1*) to actual reversal of the curvature. Curve disturbance was the only abnormality present in only one of the twelve patients showing this abnormality. Operation was undertaken in this patient after myelography disclosed a minimal root defect at C5-6 (*Fig. 2*) and at operation a firm bony ridge with no soft center was found. The density of the osteophytes was such that they did not show on the plain roentgenogram. The abnormality in this patient's lateral cervical spine x-ray (*Fig. 1*) appears as a cephalad extension of the normal transition from cervical lordosis to kyphosis, which, in this patient, appears to begin at about

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the C6-7 interspace rather than well below this point, as is normally the case. Seven other patients with curve reversal showed a similar appearance of cephalad extension of the transition mentioned above. In four patients the lateral cervical spine film revealed enough of the lower cervical and upper thoracic spine to show that the actual transition between the cervical curve in one direction and the thoracic curve in the other was occurring well below the pathological curve (*Fig. 3*), and in these instances the appearance was that of cervical gibbous affecting only one interspace. In all four patients with this picture of cervical gibbous, a root lesion was found at the site of the roentgen abnormality.

Thirteen of the fourteen patients with roentgen abnormality were found to have minimal to moderate osteo-arthritic changes at one or more cervical intervertebral disc spaces. Five of the patients had this process affecting three or more vertebrae at two or more interspaces so that in these instances suspicion was not drawn to a single space or root. One of the patients with osteo-arthritic changes affecting two interspaces associated with narrowing of the two interspaces actually had disc protrusions at both levels. Eight patients displayed osteo-arthritic processes essentially localized to a single interspace with the process on the anterior border of the vertebral bodies usually being greater than on the posterior border, where it ranged from absent or barely present to pronounced (*Fig. 4*). In all eight instances the lesion affecting the root was found at the same level as the osteophytic reaction.

In ten of the fourteen patients there was found interspace narrowing. Three of the patients with interspace narrowing had this abnormality at more than one space and in association with mild osteo-arthritic changes at the narrowed spaces. One of these patients, as mentioned above, actually had lesions at both levels, but the other two had only single lesions. The remaining seven patients with narrowed interspaces had the narrowing affecting but a single interspace, and taken as a group these showed a far more pronounced degree of narrowing than the three with multiple narrowings. In one patient (*Fig. 5*) the narrowing was of such degree as to reduce the size of the foramen and produce root symptoms in

Fig. 1

Lateral cervical spine radiograph of a patient with proven herniation of the disc between C_5 and C_6 on the right. The only abnormality present is a straightening of the cervical curve in its lower third which appears as a higher than normal transition between the thoracic hyphosis and the cervical lordosis.

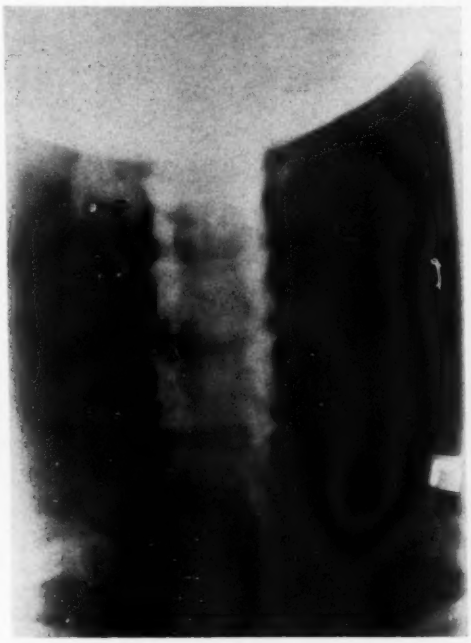

Fig. 2

Anterior-posterior myelogram of patient whose lateral cervical spine radiograph is shown in *Fig. 1*. The herniated disc on the right at the C_{5-6} interspace produced a broadening of the root sleeve complex with preservation of the upper and lower "lips." (In reproduction the sides have been reversed so the right side of the patient appears on the left in the figure.)

the absence of pressure upon the root by prominence of the disc margin, and this mechanism may have been operating in one other patient. In all seven instances of single interspace narrowing the lesion affecting the root was found at the site of the narrowed interspace. It appears significant that a total of eight patients out of fourteen had localized abnormalities in the cervical spine consisting of single interspace narrowing, single interspace osteo-arthritis, cervical gibbous, or combinations of the three, and in all eight patients with such abnormality the lesion affecting the root was found at the level of the focal abnormality.

Myelography was performed upon sixteen of the eighteen patients in the root compression group. It was not done upon the first two who were operated upon in this series. Both of these patients presented extraordinary single disc thinning with osteo-arthritic proliferation and one of them presented a cervical gibbous as well. For these reasons myelography was considered unnecessary to localize the level of herniation, though neither had pain below the elbow and a level diagnosis based upon the dermatome affected was impossible in each. Subsequent experience with cervical myelography in the next few patients seen, who did not present definite evidence as to the level of the lesion, was so satisfactory that it was thereafter used routinely, and provided information which more perfectly correlated the operative findings than any other single test or combination of tests. The technic used closely followed that described by Whitcomb and Wyatt.[1]

In fourteen of the sixteen patients subjected to myelography, evidence of cervical root involvements by abnormal prominences of disc origin were found, and in all of these the existence of such prominences was proven at operation. One of these patients who was complaining only of pain in the right arm was found at myelography (*Fig. 6*) to have bilateral root involvement with the lesion on the left side appearing larger. At operation, fragments of cartilage were recovered from both sides of this abnormal cervical disc, and without myelography the left side would certainly have been left untouched and in a condition suitable to produce trouble at a later date. One of the two patients not included in

Fig. 3

Lateral cervical spine radiograph showing a localized curve reversal at the C_{5-6} interspace associated with narrowing of the space.

Fig. 4

Lateral cervical spine radiograph showing straightening of the lower half of the cervical curve with a single narrowed interspace at C_{5-6} which is also the site of pronounced osteo-arthritic lipping on both its anterior and posterior aspects. The proven lesion consisted of a hard bony ridge at the C_{5-6} interspace compressing the left C_6 root.

the fourteen mentioned above was the patient with the greatest single disc thinning in the group (*Fig. 5*). Myelograph showed a mild transverse indentation of the dural sac at the C5-6 disc but without any evident defect in the root shadows at this level. Exploration confirmed the absence of root compression by a disc herniation and unroofing the foramen resulted in relief from all complaints in this patient who is considered to be an example of Oppenheimer and Turner's[2] discogenetic disease. The other patient not included in the group above was a woman with a cervical gibbous type of curve reversal at a minimally thinned and osteo-arthritic interspace, whose pain on different occasions was in both arms. Myelography was considered to be negative though a review of the film shows a definite central area of radiolucency without root sleeve involvement at the C5-6 interspace. At operation an osteophytic ridge was found but there was a total lack of any discernible compression of the nerve roots. Decompression of the roots by unroofing the foramina followed by spinal fusion was done, and to date the patient is entirely relieved of all pain.

It seems fair to state that in every case in which myelography was used in this series the pathologic lesion was correctly indicated. In the last patient mentioned myelography disclosed no root lesion and none was found on exploration. The central defect, to which no attention was paid at the time of myelography because of the absence of any evidence of spinal cord involvement, was shown at the time of exploration to have an anatomical basis, though it was not apparently responsible for the clinical picture. The other patient had myelographic findings of a transverse ridge opposite a tremendously thinned interspace, but without evidence of lateral root compression from disc protrusion. This situation was confirmed at the time of operation.

Our experience with myelography as related above is contrary to that of many others who find this test excessively difficult to manage or so uninformative as to be valueless. In none of the myelograms done on these patients were we obliged to put any dependence upon vague changes in the rate of flow of the media, or any

Fig. 5

Lateral cervical spine radiograph of the patient with the most pronounced interspace narrowing in the entire series. The myelogram of this patient showed no disturbance of the root sleeve complex. No significant prominence of the dorsal aspect of the disc was present on exploration. Root compression in the intervertebral foramen on the left was due to loss of altitude of the foramen.

Fig. 6

Anterior-posterior myelogram of a patient with pain in the right C_7 dermatome. Bilateral C_7 root abnormalities are present together with increased radiolucency across the C_{6-7} interspace. The right sided abnormality consists of a superior and medial displacement of an otherwise unaltered root sleeve complex. The left C_7 root sleeve complex is broadened. (The sides have been reversed in reproduction.) Herniated cartilage was removed on both sides at operation.

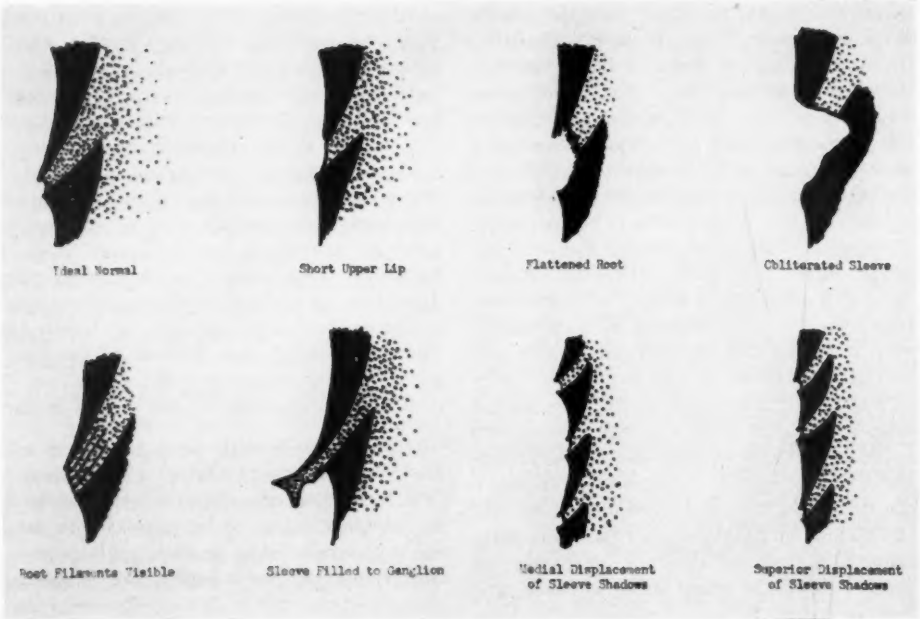

Fig. 7

Diagrammatic representation of cervical root sleeve complexes as seen on myelography. The ideal normal and three nonpathologic variations are shown on the left. Four pathologic alterations are shown on the right.

similarity of the appearance of the oil column to letters of the alphabet. All of our myelograms showed constant, reproducible, nonfilling defects or displacements of the sleeve shadow, the explanation of which required no recourse to obscure mechanisms.

Abnormalities due to lateral disc protrusions seen in cervical myelograms (*Fig. 7*) are only about five in number: (1) The appearance of broadening of the root bundle shadow within the root sleeve, which occurs when the root is flattened by compression from beneath (*Fig. 2*). (2) Medial displacement of the root and sleeve shadow complex so that all the root complexes on one side do not appear in a straight line (*Fig. 6*). (3) Superior displacement of a root and sleeve shadow complex so that the space between these shadows is not equidistant due to the presence of a prominence of disc origin below the root causing it to be displaced in a cephalad direction (*Fig. 6*). (4) Exaggeration of the normal transverse radiolucency over a disc. (5) Obliteration of the entire root and sleeve shadow complex with more or less indentation of the parent oil column (*Fig. 8*).

In the series of myelograms done in connection with our eighteen patients, broadening of the

Fig. 8

Anterior-posterior myelogram of a patient with a herniated C_{5-6} disc producing obliteration of the entire C_6 root sleeve complex with indention of the radiopaque column.

root bundle shadow was seen five times, medial displacement of the root complex was seen three times, superior displacement of the root complex was seen twice, and the root shadow complex was totally obliterated with more or less indentation of the parent oil column in seven instances. Thus, in only about one-half of the patients was the myelographic abnormality of the obvious type usually associated with extradural lesions. The rest of the patients had small defects which might be overlooked on fluoroscopy and on films if small amounts of media had been used.

SUMMARY

(1) An analysis of the roentgenograms of eighteen consecutive patients operated upon for cervical discs has been reported.

(2) Abnormalities on the plain radiograph consisted of abnormal curvature, interspace narrowing, interspace osteo-arthritis, cervical gibbous or combination of these.

(3) In many instances these findings were localized to a single interspace and the lesion affecting the nerve root was found at the affected level.

(4) Myelograms were performed on sixteen of the patients. In all instances the pathological lesion was correctly indicated.

(5) Abnormalities due to lateral disc protrusions are briefly described, and of those found in this group only about one-half of the patients had the obvious type associated with extradural tumors.

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DISCUSSION (*Abstract*)

Dr. George Ehni, Houston, Tex.—The presentation made by Dr. Moreton is, I believe, a rather convincing demonstration of the important corroborative role the radiographic findings play in the diagnosis of disturbances of the cervical intervertebral discs. The radiographic findings reported were from a series of eighteen patients who, with but one exception, were managed by one neurosurgeon and one department of radiology working in close cooperation. A good deal of other information which I cannot go into now was gained in the study of the series, but I should like to contrast the x-ray findings with certain other clinical findings in relation to the actual site of the pathologic condition.

Fifteen patients had proven herniations of disc origin, either soft or osteo-arthritic, actually compressing a root, in or just medial to the intervertebral foramen. In three others, there was a medial ridge across the interspace, but I thought the roots had adequate room over the disc, and that the cause of pain was possibly due to loss of height of the intervertebral foramen due, in turn, to a thin disc.

In fifteen patients the initial myelographic interpretations were confirmed at operation. One myelogram was called negative prior to exploration, but at exploration a transverse ridge producing increased interspace radiolucency was found, and we consider it a confirmed myelographic abnormality. Two patients were operated upon without myelography.

Focal x-ray changes occurred in a certain number and were helpful when they did occur. Dermatome hypalgesia when it was well delineated was quite accurate in determining the level of the lesion, but it occurred in only five patients.

Reflex changes in either biceps or triceps were erroneous in indicating the level of the abnormality in one or two instances.

I should like to remark briefly upon one patient, not a patient in this series of eighteen, because the case further substantiates my belief that myelography is a valuable procedure in permitting the surgeon to go right to the lesion with which he wishes to deal.

This man had a single minimally narrowed osteo-arthritic interspace without dermatome hypalgesia or other clinical findings indicating the exact level. Our expectation on the basis of these eighteen reported patients was that the herniation and the root compression were at that level.

A myelogram was done however, and at the level of the thin interspace, C5-6, there were bilateral small sleeve defects, which were due to a hard osteo-arthritic ridge, but there was a big soft cartilaginous herniation on the left side at the C6-7 space. The man's pain was all on the left side. He had a large herniation with an 800 milligram fragment of cartilage at the C6-7 space, which without myelography might not have been explored had we found the higher abnormalities on the basis of our focal x-ray changes.

As a general rule, the most successful application of the myelographic technic to the discovery of small root lesions occurs when the man who made the clinical examination of the patient and took his history is present at the time the test is done. I do not believe that myelography done as a referral procedure by a man not completely familiar with the patient's complaints and physical findings will produce as good results as when the neurologist or neurosurgeon is on hand at the time of examination, since many of these smaller root lesions require a certain degree of suspicion based upon history data and physical findings for proper interpretation. Certainly, the technical procedure of the injection of the media and its withdrawal is not something to be left to an inexperienced house officer or anyone else not able to make a clean midline puncture at the lumbosacral interspace on the first attempt, or who is unfamiliar with the maneuvers necessary to withdraw the media through a No. 20 spinal needle.

For successful cervical myelography the patient must be able to extend his neck for at least brief periods since only by such neck extension can sufficient media be

gotten into the cervical region without a portion of it entering the intracranial cisterns. At least 6 cc. of opaque medium should be used. During the transit of the medium into the cervical spine the upper extremity of its moving mass must be kept under constant observation; and one should not concern himself with observations of the movement of the main mass of the oil column in its passage through the upper thoracic region while fragments are dropping off the upper end out of sight beyond the screen. There is no surer way of ending with half the medium in the head. The one and only factor preventing medium from entering the head is the extended position of the neck, and whether the transit of the medium is accomplished rapidly or slowly is of no importance so long as the neck is held extended. In no case have we ever found it possible to maintain complete unity of the moving column through the upper thoracic region with the patient face down on the table. If enough medium is used, break-up of the oil column in transit presents no difficulty since the globules coalesce upon reaching the cervical region, and the few droplets remaining at the upper and lower extremities of the oil column are of no consequence, if enough medium is in there to make a solid column bridging two or more interspaces. For cervical myelography the medium should be injected at the lumbosacral interspace since removal there is vastly simpler than at any higher interspace.

Dr. Moreton (closing).—Dr. Ehni is always present for the fluoroscopic examination and inserts the opaque medium properly, decreases extraneous shadows due to trauma or extravasated medium. Also, consultation at this time is most important in actually deciding the significance of some of the more unusual defects, and a thorough understanding of these findings is best obtained by both parties at the time of study rather than by the radiologist's having to interpret films alone to the surgeon some days later.

OIL SOLUBLE ANESTHETICS IN PROCTOLOGY*

By A. M. PHILLIPS, M.D.
Macon, Georgia

In attempting to evaluate the results obtained in the use of any drug, personal experience is the most important factor. As many different conclusions will be drawn as there are individuals trying to arrive at a correct and unbiased decision. My results certainly are not the same as those obtained by some of you; on the other hand there are fundamental principles in technic which are or should be the same. In spite of the fact that our results may not all be the same, our purpose is the same, and that is to make the patient suffering from a rectal ailment more comfortable. This applies to the operative as well as the nonoperative patient. This same purpose should hold true in all the different branches of the practice of medicine and surgery. Cure when possible with the least pain possible; when cure is not possible, alleviate pain. This should be the aim of all proctologists since it goes without saying that rectal pain is most acute and rectal operations have always been the most dreaded. I am quite certain that the question uppermost in the minds of most individuals who contemplate a surgical operation on the anus or rectum is, "Will it be as painful as I've always heard it would be?" People have for time immemorial associated much pain and suffering with all rectal operations. This is rightly believed, since the eye itself is the only part of the human body more sensitive than the rectum. It should be the purpose of each and every one of us to try to make the patient with rectal trouble more comfortable. How many times have you had a patient after a hemorrhoidectomy say: "Doctor, I would not take a thousand dollars for my operation but I would not go through it again for anything." He is very grateful indeed, but not enough so to be willing to submit to another one. The chances are that he was given everything possible to make him comfortable but was not relieved. The next patient may say: "Doctor, there is nothing to it. I do not know why I put the operation off as long as I did. I had no pain at all." Why the difference? The answer lies in the fact that we are individuals and each one of us reacts differently to pain.

The use of oil soluble anesthetics dates back more than twenty years and there have been many advocates of it in proctology. The results obtained have varied, but like the pain referred to above, they will vary with the individual who employs them and the patient on whom they are used.

There are many conditions for which an oil soluble anesthetic has been advocated, namely: anal fissure, pruritus ani, anal or rectal neuralgia, coccygodynia and the reduction or prevention of postoperative pain of hemorrhoidectomy and other anal or rectal operations.

There are many oil soluble anesthetics on the market and each has its advocate. Benzocaine is the anesthetic agent used in most formulae since it is oil soluble. Other ingredients are phenol, benzyl alcohol, butyl para amino ben-

*Read in Section on Proctology, Southern Medical Association, Forty-Fourth Annual Meeting, St. Louis, Missouri, November 13-16, 1950.

zoate ether and so on, the amounts varying in different products. The oil employed as a base varies greatly but all are vegetable oils such as cottonseed oil, peanut oil, almond oil, peach-kernel oil and so on. I have used each of the different formulae and I know of no particular advantage of one over the other. The results obtained with the different ones have been the same in my experience.

The symptom which most frequently causes the patient to consult the proctologist is pain. By far the most common ailment causing rectal pain is thrombotic hemorrhoids. I mention this only to try to emphasize that oil soluble anesthetics have no part in this condition. They should be handled with the usual local anesthetic agent which need not be long lasting in effect.

Next in frequency is anal fissure. This as a rule is the most acute pain experienced by sufferers of anal trouble. The amount of pain may vary from a mild burning sensation to a most excruciating pain. In these cases, the injection of an oil soluble anesthetic will give prompt relief but so far as cure is concerned, the ratio is in direct proportion to the size of the fissure and the length of time since the beginning of the trouble. A small superficial fissure may heal, but in the long standing fissure with the definite thickened edges, I have yet to see one heal under silver nitrate, phenol or icthyol. The most that can be hoped for from the use of the oil soluble anesthetic is temporary relief of the acute pain until arrangements can be made to have the condition remedied by surgery. If about 5 cc. of the oil soluble anesthetic is injected directly underneath the bed of the fissure, immediate relief can be expected and will last from three to four days to two weeks. If about 2 cc. of the amount is injected directly into the sphincter muscle, the spasm will be relieved. This of course offers great relief to the sufferer temporarily.

Another condition in which oil soluble anesthetics have added greatly to the relief of the patient is pruritus ani. This is, as it always has been, the most unwelcome of all conditions in patients who visit the proctologist's office. Here again I should like to say that the ratio of expected cure is in direct proportion to the length of time this condition has existed. This is not only true of the treatment by use of injection of an oil soluble anesthetic, but also of any other method of treatment. The most that can be expected of the injection of an oil soluble anesthetic is to relieve the patient until the underlying cause can be determined and eradicated. My best results in pruritus have been obtained by what is called the clover leaf operation which is just a modification of the undercutting operation. I have been agreeably surprised however in a few cases by getting a permanent cure by the injection of an oil soluble anesthetic in conjunction with other local treatment. This is the exception rather than the rule however, especially where the condition has existed long

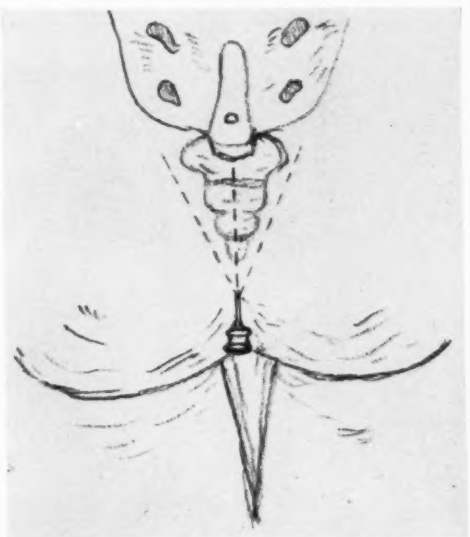

Fig. 1
Coccygodynia

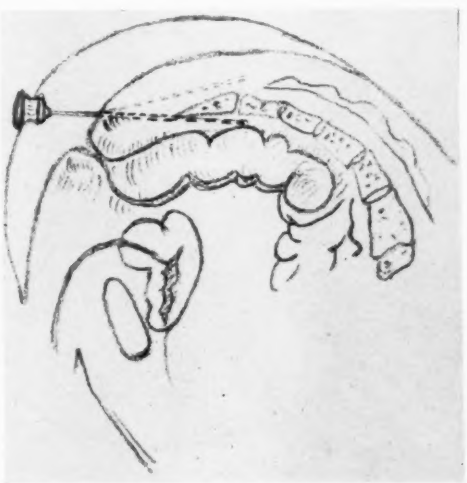

Fig. 2
Coccygodynia

enough for the terminal nerve endings to have been damaged by constant scratching. We are all cognizant of the fact that if temporary relief can be obtained and scratching is refrained from, the condition will markedly improve. This relief can often be accomplished with an oil soluble anesthetic. The procedure is somewhat lengthy, however, due to the fact that only one quarter of the anal circumference can be treated at a time and these treatments should not be closer than four or five days apart. This being true, the least amount of time that is necessary to complete treatment in the four quadrants will be about two weeks. Care must be taken not to get complete anesthesia around the anal outlet at one time. If so, an incontinence will develop which is rather embarrassing, although there is no permanent loss of control. As a matter of fact, the sensation in most cases returns all too soon, and in most cases the itching also returns.

The procedure to follow in use of the oil is to inject one quadrant at a time, employing a two-inch twenty-gauge needle and injecting the solution in a fan-like direction subcutaneously. Injection of the solution should be done on the withdrawal of the needle rather than while the needle is being inserted. The solution can be more evenly distributed and pooling can be prevented. Another important point to be remembered is that the anesthetic should not be injected too deeply but only subcutaneously because if the deep fatty tissue outside the sphincter muscle is injected, no relief can be expected. Just as important, however, is the fact that injection must not be too superficial. If so, an abscess and slough will develop. The secret of success in the relief of pruritus lies in the skill in which the solution is injected and distributed subcutaneously, thereby affecting the cutaneous nerve endings producing anesthesia. The sphincter muscle or the deep tissue should not be involved in this procedure whereas in the treatment of a fissure, injection of the anesthetic into the sphincter will relieve the muscle spasm caused by the fissure. After the injection of the anesthetic, the quadrant treated should be massaged until it is felt that an even distribution of the oil has been accomplished. This again helps prevent pooling which should be avoided.

In the treatment of rectal neuralgia and for coccygodynia, I have never been able to get the results claimed by some. This is probably due to the fact that the pain experienced by those unfortunate individuals is of the vague and indefinite type that the patient describes as high in the rectum. In the true coccygodynia, injection of the anesthetic in the posterior mid-line, directing the needle towards the coccyx and injecting the anesthetic in a fan-like direction, reaching the area lateral to each side of the coccyx as well as underneath, some relief is obtained in a few cases. In these cases a longer needle must be used in the procedure than the two-inch needle used in the technic previously described. In the treatment of rectal neuralgia and coccygodynia

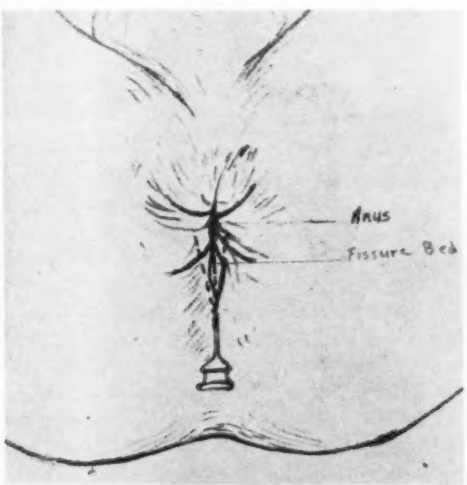

Fig. 3
Fissure

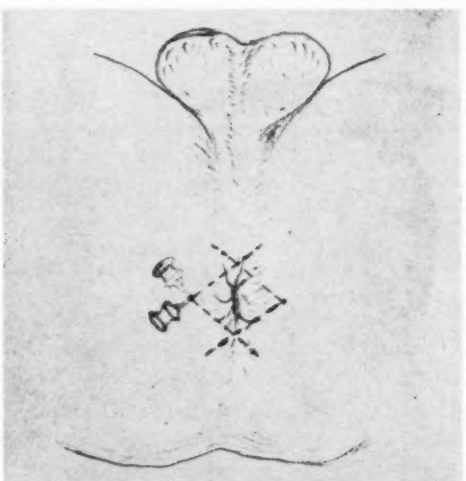

Fig. 4
Local infiltration, preoperative.

I am unable to advocate the use of oil soluble anesthetics as promising much relief.

In the prevention of postoperative pain after hemorrhoidectomy the oil soluble anesthetics play their most important role. The dread which accompanies the thought of a hemorrhoid operation usually causes the patient to put it off as long as possible. For that reason it behooves us all to alleviate as much as possible the postoperative discomfort. In a majority of the cases, this discomfort can be materially lessened and in some cases eliminated entirely. As a rule, 5 cc. of the oil anesthetic is injected in a fan-like direction lateral to the anal outlet, so that the injections overlap in the anterior and posterior midlines. This gives a better anesthesia than when the points of injection are anterior and posterior to the anal outlet. Ten cc. of the anesthetic is usually sufficient. The two-inch needle, twenty-gauge, is sufficiently long. The injections are subcutaneous and part of the solution is injected into the sphincter muscle, to afford a better relaxation of the muscle. Gentle massage then insures an even distribution. The injections are always given before operative procedure and not as some writers advocate, after operation and underneath the site of removal of each hemorrhoid. If the injections are made after completion of the operation, there will be a much greater incidence of infection and abscess formation due to the contamination of the field during operation.

When the desired results are obtained, the anesthesia will last from four to seven days. By using only 10 cc. of the anesthetic, complete sensation is not lost and the patient can experience the urge to have a bowel movement. Even if complete anesthesia is obtained, however, it

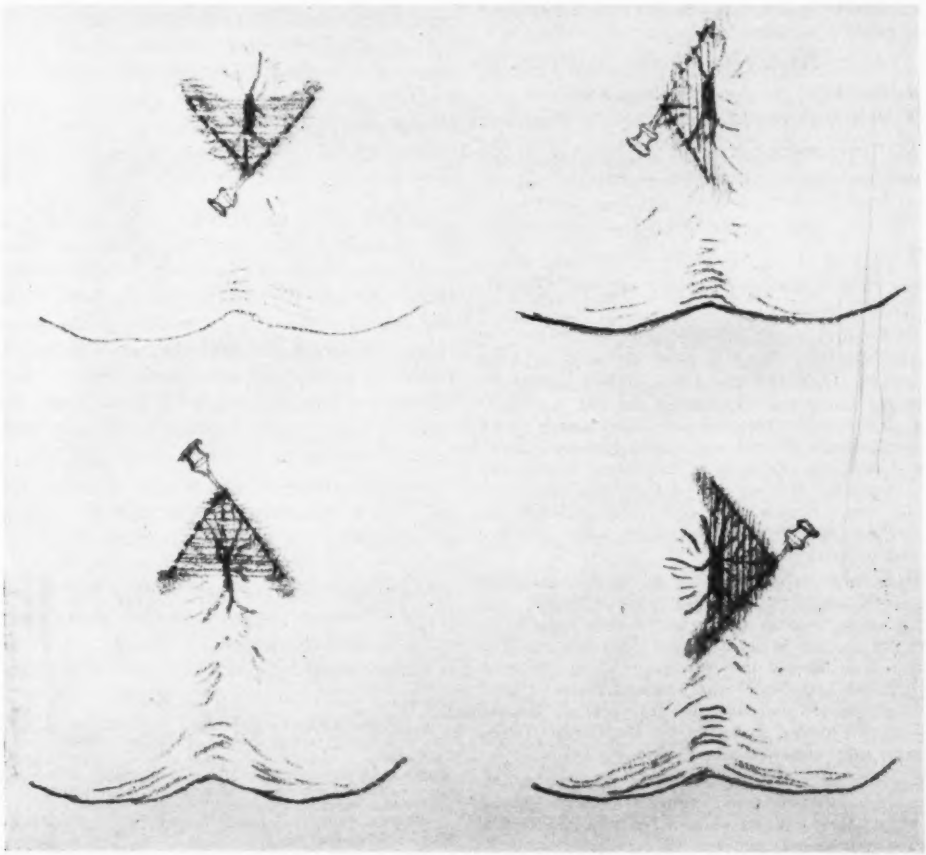

Fig. 5
Injection for pruritus.

will rarely last over three to four days, and when sensation is recovered, continence returns. If the patient is more comfortable during the first few days postoperatively, then the loss of sensation of the urge to have a bowel movement is of no significance and should not be considered.

There are a few conditions in which the use of an oil soluble anesthetic is contraindicated. They should never be used in cases of an inflammatory nature, such as ulceration, abscesses, fistulae or infection of any degree. Also injection should never be made into scar tissue of any kind, for abscess formation will invariably follow.

SUMMARY

(1) An attempt is being made to make the proctologic patient more comfortable.

(2) Oil soluble anesthetics play a part in accomplishing this.

(3) Fissures, pruritus ani and postoperative hemorrhoidectomies are the conditions in which most relief is obtained.

(4) Coccygodynia and rectal neuralgia are the least helped.

(5) The technics have been briefly described.

(6) The contraindications of the use of oil soluble anesthetics have been given.

DISCUSSION (*Abstract*)

Dr. Mark M. Marks, Kansas City, Mo.—Oil soluble anesthetics have had their rise and fall, and to many, they are still unknown.

This excellent paper is timely because it shows the need for continued search to lessen postoperative pain.

Anesthetics dissolved in an oily vehicle should be recognized as analgesics because of the lack of diffusibility. It is true that there are scant differences in action between most of the commonly used formulae. However, saponifiable oils such as cottonseed, peanut and corn, should not be used since in their dissolution they produce severe fibrosis. The safe vehicles removed by phagocytosis are oils expressed from sweet almonds, raisin and sesame seeds.

Sixteen years experience with oil soluble analgesics have taught me to guard against muscle injection. The passage of a 20-gauge needle into muscle tears sufficiently to produce hemorrhage and delay healing. The medication is injected into the spaces about the anus to affect the branches of the pudendal nerve. I have long ago stopped injecting for coccygodynia because removing the causes, as taught by Dr. George Thiele, has given more consistent, good results.

An additional useful application for the oil bearing analgesics is following severe coccygeal trauma. During one winter, three patients were treated who had slipped on ice and produced fractures. Pain and shock rapidly responded after pericoccygeal injection under intravenous anesthesia.

Dr. Phillips emphasized the need for good surgical procedures. The use of the pain-relieving injections should be done with care and understanding. During my army career, I constantly used oil soluble material for supplementary pudendal block following anorectal surgery with satisfactory results and have continued since. To prevent pooling it has been my practice to mix 2 per cent procaine hydrochloride with oil. Ten cc. of each are placed in the same syringe and bounced against the thenar surface of the opposite hand to emulsify it. After surgery, this emulsion can easily be injected through four quadrants and gently massaged into the surrounding tissue.

Two contraindications for the use of these materials are, (1) in those who have evidence of poor venous return as in varicosities of the pelvis and extremities and (2) in cases of the aged whose circulation is impaired.

TRANSFUSION IN THE MANAGEMENT OF CLOSED HEAD INJURY*

PRELIMINARY REPORT

By EDMUND A. SMOLIK, M.D.†
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and
FRANCIS P. NASH, M.D.§
St. Louis, Missouri

In this report we wish to call attention to the hematologic changes occurring in cerebral trauma and to emphasize the beneficial effects of whole blood therapy in cases of closed head injury. We have selected only those cases of closed head injury in which cerebral trauma was the sole factor in producing the clinical picture. Cases of cerebral trauma associated with shock, fractures of long bones, visceral injury or extensive lacerations causing blood loss were excluded.

A closed head injury is one in which there has been an alteration of the head by force and in which the protective skull is not broken to give access to the enclosed nervous structures.[1] A simple linear fracture may or may not be associated. In most instances there is either a mild or moderate concussion. Clinically, concussion is characterized by a transient loss of conscious-

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*The cases studied are from the Neurosurgical services of St. Louis University and Associated Hospitals, City, County, Jewish and De Paul Hospitals, St. Louis, Missouri.

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ness, from a few moments to several minutes followed not infrequently by vomiting, dizziness, confusion or headache.[2] Such injuries manifest no gross morphologic or microscopic changes within the brain.

Trauma to the brain produces a generalized disturbance within the nervous system. Various specific functions of the brain, for example, glucose and water metabolism, may be affected to a greater or lesser degree.[3]

Recently Mardomingo[4] and Wanke[5] have called attention to the widespread autonomic effects of cerebral trauma. The former noted alteration in the red blood cell count in 46.1 per cent of 53 cases studied, but without any definite trend. The reason was that only initial red counts were in many instances recorded and no correction for hemoconcentration was made. Particular emphasis was placed on the leukocyte changes.

In our series of 68 cases of closed head injury, 40 or 58.8 per cent showed drops in the red blood count to levels well below the accepted normal values. In some instances counts as low as 2.5 million red blood cells and hemoglobin values ranging between 5.75 and 12.0 grams were noted. A few illustrative cases show the characteristic changes and indicate the necessity for whole blood therapy.

Case 1 (Table 1), St. Louis City Hospital, No. 5692.—A five-year-old boy entered the hospital June 15, 1948, with a history that he had fallen two stories to a concrete wall twenty minutes before admission. On entry into the hospital blood pressure was 100/70, pulse 80, respirations were 25. He was semicomatose. There was a small laceration of the forehead and swelling of the right parietal area. X-rays revealed a right parieto-occipital fracture. The neurologic examination was otherwise negative. He was discharged August 17, 1948. The blood picture is shown in the table.

Date	Hgb.	Rbc.	Ht.	Prt.	Wbc.	Treatment
6-15-48	10.0	3.7	29	6.2		Oxygen tent because of cyanosis. No fluids
6-16-48						250 cc. plasma 250 cc. of blood 1000 cc. of 5 per cent glucose
6-17-48	11.0	4.1				250 cc. of blood and fluids totalling 1,500 cc. in form of glucose and Ringer's solution
6-18-48						1,500 to 2,000 cc. intravenous and subcutaneous fluids
6-19-48						1,500 to 2,000 cc. intravenous and subcutaneous fluids
6-20-48	10.0	6.8	30			250 cc. of blood and fluids
6-28-48	11.0	4.9	33	7.8		Now alert, taking oral feedings
7-14-48		5.1			9,800	Increasingly mentally oriented

Table 1, *Case 1*

Case 2 (Table 2 and Fig. 1), Jewish Hospital, No. 202812.—This was a twenty-eight-month-old girl, admitted on October 24, 1950, with a history that twelve hours previously she had fallen backward off a chair at 7:00 p.m. At 1:00 a.m. on the following day the baby vomited. The parents noticed that the eyes turned to the left, that she was unresponsive, and then there was a generalized convulsion. One hour later there was twitching around the mouth and she was admitted to the hospital at 8:00 a.m. on the morning following the injury. Blood pressure was 124/75, pulse 110, respirations were 18, temperature was 100.6.° Another blood pressure recording was 108/60. On October 24, 1950 spinal fluid showed no cells, Pandy was negative, fluid was clear, total protein was 44 mg. per cent.

By October 28, the child was perfectly alert, the color was excellent, she was brisk and playing instead of being restless and irritable. On the subsequent day, October 29, 1950, she took a normal amount of oral feedings and was discharged on October 31, 1950. The electroencephalogram showed a dysrhythmia consistent with a concussive state. The striking improvement in this child's appearance, irritability, and listlessness after she received the three transfusions was very dramatic and exemplified again the necessity of whole blood therapy in the immediate postconcussive state.

Case 3 (Table 3), St. Anthony's Hospital, No. 564.—A one-year-old boy was admitted on January 28, 1948, and discharged on February 10, 1948. There was a history that the previous night the child fell backward striking the back of his head on the floor. He was irritable, cried and vomited three times. He was lethargic. His blood pressure was 128/75, pulse 100, temperature 99.° He cried. The pupils were equal. The neurologic examination was negative. This child made an excellent recovery and was discharged on February 10, 1948.

Date	Hgb.	Rbc.	Ht.	Prt.	Wbc.	Treatment
10-24-50	5.75	4.2	30		12,850	250 cc. of lactated glucose
10-25-50	6.25	4.04	39		12,100	250 cc. of Ringer's twice a day. 200 cc. of whole blood and began to take some liquids orally
10-26-50	7.5	4.58	30		9,700	200 cc. of blood, 800 cc. of oral feedings
10-27-50	10.0	5.6			7,750	200 cc. of blood, taking all feedings
10-28-50	12.9	5.2			7,000	
10-31-50	15.0	5.2	43		7,500	Discharged

Table 2, *Case 2*

Case 4 (*Table 4* and *Fig. 2*), *De Paul Hospital.*—This three-year-old boy was admitted on July 21, 1949, and discharged on August 12, 1949. There was a history that he had been in an automobile accident, unconscious for one or two hours, and was given 250 cc. of fluid in the emergency room. He had multiple abrasions. On July 26, 1949, x-rays revealed no evidence of skull fracture. There was a left hemiplegia on entry and the child remained unconscious for ten days. The blood pressure remained within normal range, with a pulse running at a level of 100. He was discharged on August 12, 1949, completely conscious and using the left side, completely recovered.

Date	Hgb.	Rbc.	Ht.	Prt.	Wbc.	Treatment
1-29-48	7.0	2.76			14,700	300 cc. of 5 per cent glucose
1-30-48						300 cc. of 5 per cent glucose
1-31-48	6.0	2.54			9,600	300 cc. of 5 per cent glucose
2- 1-48						300 cc. of 5 per cent glucose
2- 2-48	3.94					Following transfusion of 150 cc. of blood, 300 cc. of 5 per cent glucose

Table 3, *Case 3*

Date	Hgb.	Rbc.	Ht.	Prt.	Wbc.	Treatment
7-21-49	5.5	2.31			12,800	250 cc. of blood, 500 cc. of 5 per cent glucose
Later	7.1	4.10			15,400	
7-22-49	7.1	3.91			8,500	250 cc. of blood plus parenteral fluids to the amount of 1,000 cc. in tube feedings
7-23-49	9.4	5.38			12,000	
7-24-49	9.7	4.83			10,250	
7-25-49	8.4	4.39			8,550	200 cc. of blood
7-26-49	9.0	4.66			9,000	Received tube feedings
7-27-49						200 cc. of blood plus tube feedings
7-28-49	9.7	4.90			9,400	Tube feedings
7-29-49						Tube feedings
7-30-49						Tube feedings, beginning to awake, using the left side slightly
8- 1-49	9.0	4.40			7,250	Beginning to eat and responding completely

Table 4, *Case 4*

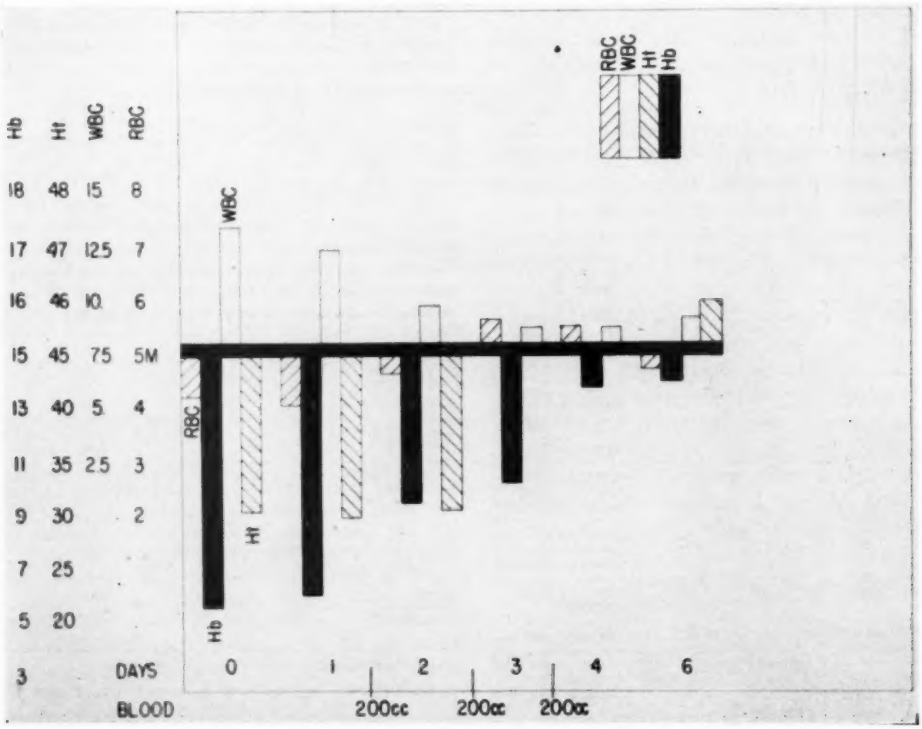

Fig. 1, *Case 2*

Case 5 (*Table 5* and *Fig. 3*), *St. Louis City Hospital, No. 96043.*—A thirty-year-old man was admitted on March 26, 1949, and discharged April 12, 1949. There was a history that his automobile had hit a tree. Two other passengers were killed. He was brought into the hospital in a semicomatose state. He responded to painful stimuli. Blood pressure was 110/60, temperature 100,° respirations 24, pulse 110. X-rays revealed no evidence of skull fracture. The neurologic examination, except for the semicomatose state, was negative. April 12, 1949, he was discharged in excellent condition.

Case 6 (*Table 6*), *St. Louis City Hospital, No. 99328.*—A two-year-old boy was admitted on July 10, 1949, with a history that he had fallen out of a third story window. He was unconscious briefly, vomited three times and was admitted to the hospital with pupils contracted and gross nystagmus. The neurologic examination otherwise was negative except that the patient was unresponsive to commands and was apathetic. The temperature was 37.8,° pulse 144 and blood pressure 150/100. An electro-encephalogram showed paroxysmal bursts of activity, consistent with a concussive basis for the patient's complaints.

Case 7 (*Table 7* and *Fig. 4*), *St. John's Hospital.*—A fifty-nine-year-old man was admitted on May 25, 1949, and discharged on June 8, 1949. There was a history that four days previously he had been struck on the head. He was comatose and cyanotic and had signs of

Date	Hgb.	Rbc.	Ht.	Prt.	Wbc.	Treatment
3-26-49	13.0	4.57			32,950	
8 hours later 3-26-49	11.0		33	5.8		2,500 cc. of 5 per cent glucose
3-27-49						2,000 cc. of 5 per cent glucose
3-28-49	12.8					Approximately 2,000 cc. of parenteral fluids
3-31-49	9.5		28	6.5	14,500	Parenteral and oral fluids at this time
4- 3-49	9.0	3.11			14,500	500 cc. of blood and normal oral intake
4- 5-49						500 cc. of blood and normal oral intake
4- 8-49	13.5	3.76			10,100	Normal oral intake
4- 9-49						500 cc. of blood and normal oral intake
4-11-49	15	4.01				

Table 5, *Case 5*

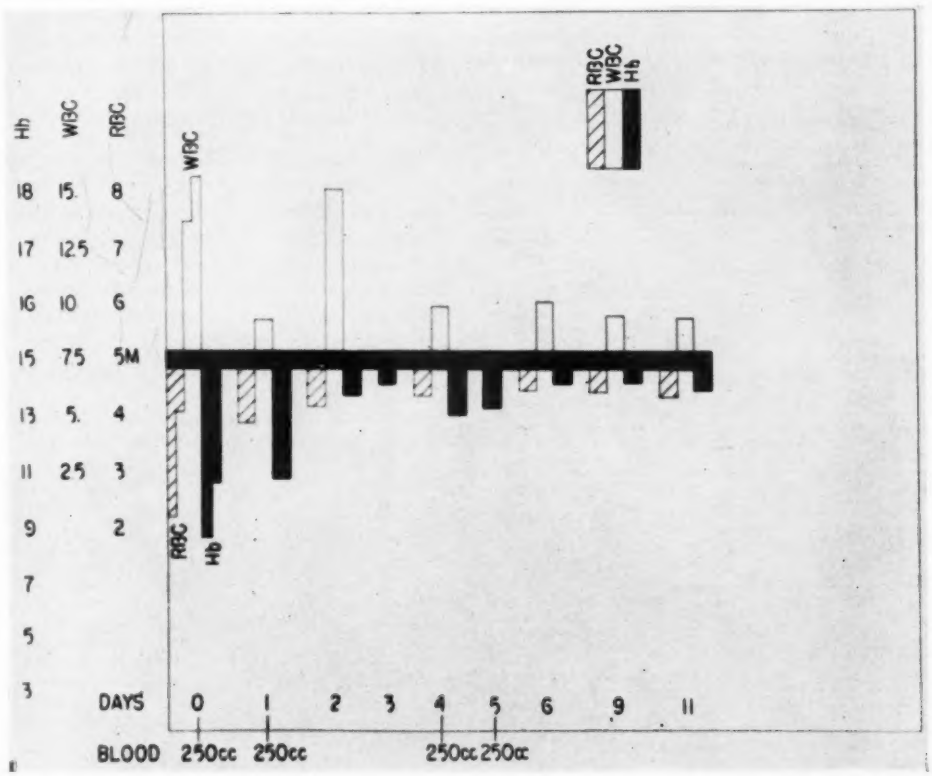

Fig. 2, *Case 4*

decerebrate rigidity. On May 21, 1949, he was operated upon for a subdural hematoma and was then transferred to St. John's Hospital.

Case 8 (Table 8), St. Mary's Hospital, No. 50-7263.—This girl, age five years, was admitted at 10:40 p.m. on September 5, 1950, with a history of having fallen at 6:00 p.m. She was not unconscious but had vomited twice. Neurologic examination was negative. She had fallen off a porch to concrete. There was no bleeding but the child was somewhat listless and apathetic. Her blood pressure was 100/70, temperature 99.8,° pulse 88, respirations 24 and the blood pressure remained constant at all times, the average being approximately 110/80. She was discharged in excellent condition, fully recovered, alert and without any complaints.

Date	Hgb.	Rbc.	Ht.	Prt.	Wbc.	Treatment
7-10-49		5.37	15.5		11,250	300 cc. of 10 per cent glucose, 150 cc. plasma, oxygen tent
7-11-49	8.5		24.0	5.7		250 cc. of blood, 400 cc. of 5 per cent glucose
7-12-49	11.5		34.0	7.2		800 cc. of 5 per cent glucose, 200 cc. orally
7-13-49						350 cc. of blood, 800 cc. of 5 per cent glucose
7-14-49	17.5		53	5.8		800 cc. of 5 per cent glucose and oral liquids
7-15-49						500 cc. of 5 per cent glucose and soft diet with liquids
7-16-49	18.0		55	6.2		400 cc. of 5 per cent glucose and oral fluids. From then on he was able to take nourishment
7-21-49	17.3		51	6.8		
8-11-49	16.5		49	6.2		Patient discharged

Table 6, *Case 6*

Date	Hgb.	Rbc.	Ht.	Prt.	Wbc.	Treatment
5-26-49	10.05	3.31			6,900	2,500 cc. of 5 per cent glucose
5-27-49						2,000 cc. of 5 per cent glucose, 1,000 cc. of amigen®
5-28-49	9.5	3.17				1,000 cc. of 5 per cent glucose, 1,000 cc. of 5 per cent saline, 1,000 cc. of amigen®
5-29-49						500 cc. of blood, 3,000 cc. of parenteral fluids
5-30-49						500 cc. of blood, 3,000 cc. of parenteral fluids
5-31-49	11.0	3.54			10,650	500 cc. of blood, 3,000 cc. of parenteral fluids
6- 1-49						1,000 cc. of parenteral fluids, 1,500 cc. orally
6- 2-49	10.8	3.46			8,600	1,000 cc. of 5 per cent glucose and saline, oral feedings up to 2,000 cc. Thereafter he took daily feedings
6- 4-49						500 cc. of whole blood
6- 7-49	12.0	3.85			8,400	

Table 7, *Case 7*

DISCUSSION

These cases demonstrate the significant drops in hemoglobin and red blood counts which require correction by whole blood replacement therapy. Heretofore concern with cerebral edema has lead to the almost uniform application of active dehydration therapy and limited fluids. Such patients have been subjected to hypertonic glucose solutions by vein and magnesium sulphate retention enemata. Actually there is considerable doubt as to the efficacy of such dehydrating agents and disagreement exists as to their ultimate beneficial effects on the cerebral spinal fluid pressures as shown by Bragdon[6] and others.[7] According to Pilcher,[8] the optimum fluid intake is a moot question. He recommends the use of an average of 2,000 cc. of fluid in a twenty-four-hour period.

The mechanism of the anemia is not understood satisfactorily at the present time. The studies of Rosenow,[9] Houssay[10] and Hoff[11] particularly suggested that alterations in the composition of blood occur on central stimulation. This work was carried out on experimental animals and the effect of central stimulation on the white blood cell elements particularly was studied. In a comprehensive paper, Lucia and

Date	Hgb.	Rbc.	Ht.	Prt.	Wbc.	Treatment
9- 5-50	10.5	2.75				Given no fluids but vomited twice
9- 6-50	11.2	3.9	31			500 cc. of 10 per cent glucose, 250 cc. of oral feedings
9- 7-50	10.6	3.8	29			1,500 cc. oral intake
9- 8-50						1,500 cc. oral intake
9- 9-50	10.3	3.75	31			500 cc. of blood 1,000 cc. of oral intake
9-10-50	15.2	5.10	45			

Table 8, *Case 8*

Marasse[12] have summarized the relationship of the central nervous system and hematopoiesis. Vaughn,[13] studying the blood picture of air raid and battle casualties, was impressed by the fall in hemoglobin levels which occurred in the first fortnight after injury. He reported an anemia that was out of proportion to the amount of blood lost at the time of the incident. He reported studies on fourteen cases of varying fractures of the femur, malar bone, patella, burns of the face, fractured pelvis, multiple lacerations, compound fractures of the skull and lacerated eye, and so on. No definite isolated cases of head injury were studied. It was suggested that the anemia thus occurring was not due to blood loss or hemolysis but to a disturbance of hemoglobin synthesis dependent upon disordered liver function. Such a theory seems untenable with reference to the cases studied here, as the drops appear within such a brief period following the injury as to be almost instantaneous, and would seem from theoretical grounds to be unassociated with hepatic injury. However, the marked effect on the vegetative nervous system as evidenced by vasomotor, hematologic and metabolic changes following stimulation or injury in the hypothalamic and medullary regions of the brain, suggests the possibility of immediate changes in the vascular bed and hemodilution incident to severe cerebral trauma. The similarity between the hemoglobin drop and that produced by burns suggested to Vaughn the possibility that there may be a qualitative relationship. Further studies certainly are indicated of the mechanism of the anemia of trauma. The authors[14] were impressed by the association of anemia with the fall of albumin and rise of globulin and fibrinogen, without alteration of the total circulating protein. These changes appeared to be associated with an increase in nitrogen excretion.

Some conclusions regarding the mechanism of circulatory failure following head injury were reached by Denny-Brown and Russell.[15] Their work confirmed earlier (1894) conclusions of Polis:[16] that head injury resulted in death in those cases in which vasomotor failure followed a period of increased activity of this center. Respiratory failure was also considered a factor. They described vasoconstriction with moderate injuries and vasodilatation with severe cerebral

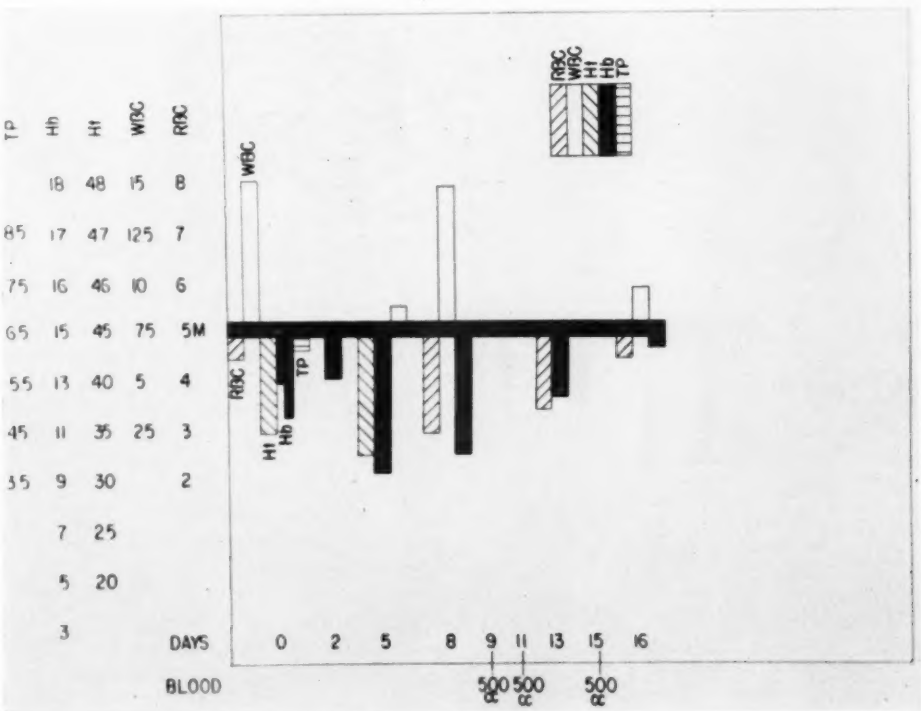

Fig. 3, *Case 5*

injuries. It was shown that medullary failure could result without any gross lesion. Their summary of the pathology of severe head injury postulated a state of continuous vasodilatation and hypotension due to prolonged vagoglossopharyngeal stimulation which counteracted the pressor effect of injury to the vasomotor center. Gurdjian and Webster[17] concluded from their work on experimental head injury, that the circulatory failure was due to paralysis of the vasoconstrictor center with resultant vasodilatation. They could not agree with Denny-Brown and Russell that vagoglossopharyngeal stimulation and active vasodilatation was necessarily present.

Schendorf[18] and his group have shown laboratory and clinical evidence that, following cerebral concussion, varying degrees of oxygen deficiency occur. This is the result of the following processes:

(1) Stagnant anoxia secondary to the hypotensive, sluggish circulation.

(2) Anoxic anoxia, due to possible concomitant damage to the respiratory center.

(3) Relative anoxia in cases of cerebral trauma developing a secondary hyperthermia, thus increasing tissue oxygen demands.

To the listings of Schendorf we would add:

(4) Anemic anoxia, due to the lessened oxygen carrying capacity of the blood secondary to the erythrocyte loss of hemoglobin, hematopoietic depression, or hemodilution.

These same investigators described their studies of arterial oxygen concentration in a series of patients suffering from head injury. They showed that there was a lessened oxygen saturation of the blood that varied from 5 to 44 per cent below the normal. Clinically, they observed the markedly beneficial effects of intensive oxygen therapy. No mention was made of the erythrocyte counts of the patients studied.

The oxygen requirement by the central nervous system is reflected in its arterial supply which is 25 per cent of the cardiac output.[19] Arteriovenous oxygen differences in cerebral circulation re-emphasize the need by this tissue of adequate oxygen. The important substrate of cerebral

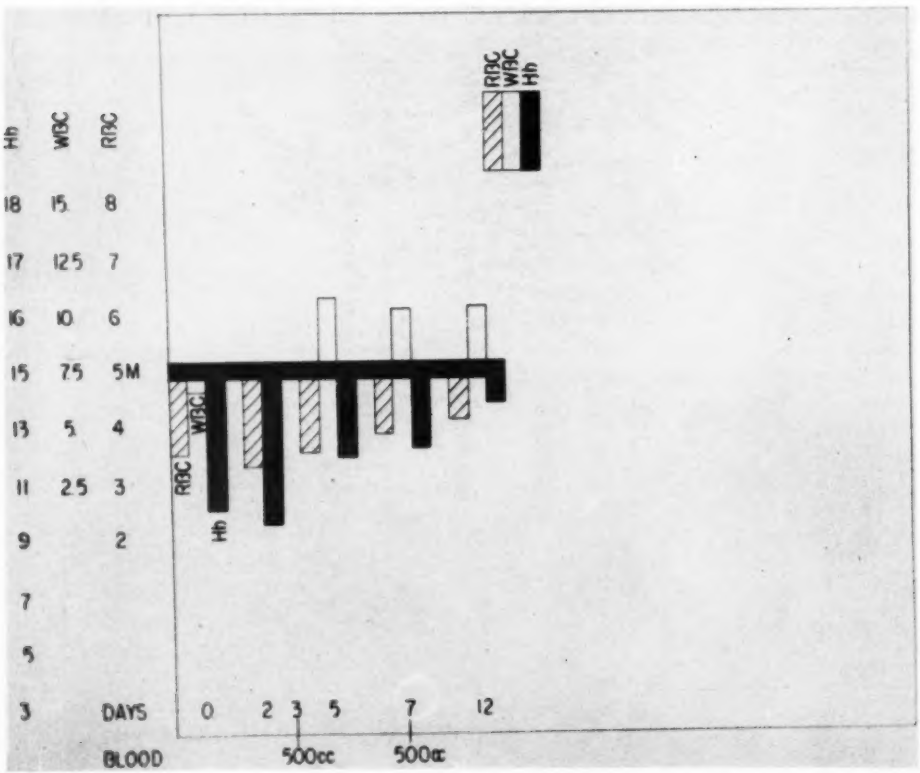

Fig. 4, *Case 7*

oxidation is dextrose. Dextrose after a series of reactions is transformed into pyruvic acid. When adequate amounts of oxygen and required coenzymes are available, the pyruvic acid is oxidized to carbon dioxide and water. In the absence of adequate amounts of oxygen the pyruvic acid is changed into lactic acid.

Stone, *et alii*[20] conducted studies concerning the chemical changes in the brains of cats following injury. They reported that lactic acid and inorganic phosphates increased, while phosphocreatine decreased in brains subjected to injury by anoxia. Cummings[21] also showed that the level of inorganic phosphates was increased in the plasma after cerebral trauma.

The possible altered circulatory status developing following cerebral trauma could be self-perpetuating. The initial trauma produces a series of peripheral vascular changes, namely: vasoconstriction and vasodilatation. There is some evidence to support the doctrine of "trapped blood" resulting from the above. At any rate circulatory erythrocytes are lost. This together with the changes in circulatory dynamics results in lowered oxygen availability to the tissues. This state of hypoxia encourages a progression of events that result in furthered circulatory embarrassment. The effect is probably most marked upon such an actively respiring organ as the brain. Its altered function due to hypoxia is manifested systemically.

THERAPY

The general supportive measures given the patient in the shocked state are fluids. Specifically, we have no more direct approach toward the restoration of normal physiologic function than to increase the oxygen availability to the tissues. The administration of whole blood increases the oxygen carrying capacity of the circulating blood. Also, it increases the circulating blood volume, thus tending to restore normal circulatory dynamics. In addition, experiments of Goldberg and Fine[22] have shown that whole blood transfusions seem to improve the absorption rate of water and glucose from the small intestine. This would increase the amount of circulating glucose available for metabolism. The increased water absorption allows a ready route for the re-establishment of depleted levels of interstitial fluid which were utilized for hemodilution.

From a practical point of view, however, and irrespective of the theoretical aspects of the etiology of the anemia, it is important to emphasize that these patients should receive adequate fluids and particularly whole blood replacement therapy to correct the obvious anemia.

SUMMARY

(1) This report puts on record the incidence of profound anemia observed in cases of closed head injury.

(2) The marked beneficial effects of whole blood therapy in the management of cerebral trauma is emphasized.

(3) Various physiologic changes are listed as being possible factors in the development of this anemia.

(4) Further investigation into the physiologic phenomena is indicated.

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DISCUSSION (*Abstract*)

Question.—What, if any, were the associated injuries to these patients other than the head injury? What are the normal hematologic pictures in the normal patient over a period of hours during wakefulness and sleep? What are the hematologic changes in injuries other than cerebral?

Dr. Smolik.—There were no associated injuries. This was specifically our criterion: that there should be no associated shock, no lacerations, no hemorrhage.

As to the normal hematologic picture during wakefulness and sleep: to my knowledge, there is a relatively minimum and insignificant variation. The accurate figures I cannot give you at this time.

What are the hematologic changes in injuries other than cerebral? The only data that I recall from the literature on this subject is the work of Vaughn who studied air raid casualties in Great Britain in 1945. He also noted a drop in the hemoglobin and red blood count that persisted and was significant. It was their idea that this anemia was in some way related to injury of the liver.

Question.—How soon after injury do you give blood transfusion?

Dr. Smolik.—We frequently give transfusions to the patients as they enter the emergency room. Obviously, not all concussion cases will follow the same pattern, whereby they all require blood. In only 56.8 per cent of a series of sixty-eight cases of closed head injury did we find this type of drop.

Question.—Does a blood transfusion produce any dramatic clinical improvement in an unconscious or semicomatose patient after a head injury other than the raising of the hemoglobin and red blood cell levels?

Question.—Do you use the various blood components as cell suspension to correct anemia without disturbing blood volume and plasma, to alter the blood volume alone when necessary and when there is no anemia?

Dr. Smolik.—We deliberately entitled this presentation "Preliminary." There is much basic work that has to be done to explain what actually happens. We have seen a great volume of civilian head injuries in which such changes have impressed themselves on us. For example, a young girl was sent to us with a closed head injury, who had a right hemiparesis and a hemiplegia of ten days' duration. We checked the blood count and it was in the order of three and a half million with a hemoglobin of approximately 68 per cent. We gave this girl a transfusion. Two days later we transfused her again and she was dramatically able to use the leg completely and the aphasia and mental retardation cleared.

Yes, I certainly believe that plasma should be utilized. I believe in the same attitude that has been demonstrated dramatically and forcibly by Dr. Elman in his work upon parenteral alimentation in general surgery. Some work of that order has to be done in reference to head injuries. Specifically we have not used cell suspensions nor have we so far made observations on the blood volume alterations.

POSTTRAUMATIC ISCHEMIC INFARCTION OF THE KIDNEY DUE TO ARTERIOSPASM*

A CLINICOPATHOLOGICAL AND EXPERIMENTAL STUDY

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In 1944, Kimmelstiel[1] reported fifteen cases of ischemic infarctions of the viscera which he attributed to focal vascular spasm caused by accidental trauma in some cases and by operative trauma or shock in others. Since this report we have studied four clinical cases of posttraumatic infarction of the kidney in which we believe the etiologic factor to be arteriospasm. The reasons submitted to support this belief are: (a) the failure to demonstrate mechanical vascular occlusions to explain the infarcts, coinciding with the experiences of Neuberger,[2] von Marenholtz[3] and Frank and Jaffe;[4] (b) the failure to demonstrate a source of emboli from the lungs or heart, or a septal defect in the latter which would permit passage of an embolus from the systemic venous to the systemic arterial tree; (c) the fact that the infarctions were frequently incomplete which is not likely to occur with thrombotic or embolic occlusion; (d) the fact that traumatic segmental angiospasm of the larger arteries of the extremities has been directly observed at surgery;[5 6 7] (e) the fact that renal cortical necrosis has been produced by prolonged injections of vasospastic drugs;[8 9] and (f) the fact that we have been able to produce infarcts in the experimental animal by both trauma and a vasospastic drug. The demonstration of an absence of thrombi and emboli was based on a dissection of the main arterial tree, together with microscopic sections

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*The authors wish to express indebtedness to Dr. Paul Kimmelstiel for stimulating their interest in this pathological entity and for the use of cases from his files, to Dr. Hamilton W. McKay for originally arousing their interest in the problems concerning the injured kidney, and to Dr. Russel Fisher, Medical Examiner of the City of Baltimore, for permission to use clinical *Case 3*.

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taken from serial thin blocks from the area of and surrounding the infarcts.

It is the purpose of this paper to (a) review the relevant medical literature, (b) to report the clinical and pathological findings in the four clinical cases mentioned above, and (c) to describe the infarcts which we have produced experimentally in the rabbit by trauma alone and by the administration of adrenalin hydrochloride.

REVIEW OF THE LITERATURE

Posttraumatic infarction of the kidney has received scant attention in the literature. The first case on record is that of von Recklinghausen[10] (1861). The meager autopsy description of the kidney leads us to assume that there was thrombosis of the pedicle vessels. Neuberger[2] (1927) reported two cases of posttraumatic renal infarctions in which there were no demonstrable arterial occlusions in serial sections. He noted thrombi in the renal veins which he believed to be of more recent origin than the infarction and concluded that the infarcts were due to a traumatic angiospasm similar to the traumatic segmental arterial spasm which he had noted in vessels of the leg as a result of war injuries. Von Marenholtz[3] (1928) reported a similar case with essentially identical conclusions. Frank and Jaffe[4] (1933) reported a case in which vascular injury and thrombosis were apparently absent; histologic study showed necrosis and hemorrhage of the renal cortex. They assumed vascular spasm to be the cause of the infarcts. Regan and Crabtree[11] (1948) reviewed ninety cases of renal infarct in the literature and added four cases of their own. Of these ninety cases only three were traumatic infarcts. These authors stated that traumatic infarction of the kidney depends on direct injury to the renal vessels. A review of these three cases reveals that there was definite thrombosis of the vessels in two of the cases; that of Barney and Mintz[12] (1933) and that of Hirshberg and Soll[13] (1942). In the third case, that of Rexford and Connolly[14] (1945), there is no specific mention either of the presence or of the absence of thrombi in the renal vessels. Finally, Meeter and Schwartz[15] (1950) reported a case diagnosed as old traumatic infarction of the kidney in which no note is made as to the status of the renal vessels.

There are no reported attempts to produce traumatic ischemic renal infarction experimentally. Stirling and Lands,[16] in an experimental study of the various types of renal injury in cats and dogs, found necrosis at the site of injury in two animals. However, there was actual rupture of the kidney in these cases and one would presume that there was probably disruption of the vascular supply.

Cases of bilateral acute renal cortical ischemic necrosis, which we believe is a pathological lesion probably related to traumatic unilateral ischemic infarction of the kidney, have been reported by Furtwaengler[17] (1927), Helwig and Orr[18] (1932), Helwig and Schutz[19] (1932), Husfeldt and Bjering[20] (1937) and Penner and Bernheim[8] (1940). The latter authors found the lesion to be associated in their cases with shock of varied causation. They were able to produce similar lesions in the dog by injections of adrenalin. They felt that the vasospasm which occurs in shock is of sufficient intensity and duration to result in ischemic necrosis. Byron[9] (1937) had produced similar lesions in the rat with vasopressin. Helwig and Schutz[19] ascribed the renal cortical necrosis present in their six cases of traumatic rupture of the liver to the action on the kidneys of some potent toxin produced in the liver by hemorrhagic necrosis. Furtwaengler[17] attributed this renal cortical necrosis to an angiospasm caused by the presence in the blood stream of "toxins" derived from the traumatized liver. Husfeldt and Bjering[20] felt that the renal lesions were related in some way to shock which was present in all of their cases, but that the exact mechanism was obscure.

Trueta and his associates[21] (1947) produced unilateral renal cortical ischemia in the rabbit by placing a tourniquet about the ipsilateral lower extremity and by electrical stimulation of the ipsilateral splanchnic nerve. Goodwin, Sloan and Scott[22] (1940) found that this ischemia could be intensified by direct stimulation of the nerve plexus surrounding the renal artery.

CLINICAL CASE REPORTS

Case 1.—G. D., C. M. H. No. 60174, a 15-year-old white girl, was admitted on the general surgical service February 2, 1947, an hour following her injury in an automobile accident. She was in shock at the time with a blood pressure of 68/50 which responded to blood transfusion with a rise to 84/50 in thirty minutes. Four hours later, her blood pressure again fell to 64/34 but again rose to 80/50 after she received more blood. Her blood pressure was maintained thereafter at levels between 90 and 130 systolic until her death 36 hours after admission. When she was first seen, the abdomen was rigid and there appeared to be generalized abdominal

pain on palpation, being most marked in the right flank. A catheterized urine specimen was negative on admission but was blood tinged 12 hours later. A specimen obtained just prior to death contained only 25 erythrocytes, an occasional leukocyte and a few granular casts per high powered field. Abdominal exploration was thought inadvisable in view of the severe head injury, multiple rib fractures and pelvic fractures.

Pathology Report.—In addition to the numerous skeletal fractures, there were hyperemia and meningeal hemorrhages over the left occipital lobe of the brain, a slight hemoperitoneum, capsular tears of the spleen, a small rupture of the liver parenchyma with an adjacent small area of ischemic infarction, a small area of hemorrhage in the right adrenal medulla, retroperitoneal hemorrhage on the right and scattered small ischemic infarcts of the right kidney. The renal capsule stripped easily revealing a surface free of laceration. At the upper pole were two irregular, slightly elevated, moderately firm, sharply demarcated grayish yellow areas measuring roughly a centimeter in diameter each. On section these lesions were rhomboid-shaped with their bases at the periphery and they were composed of homogeneous grayish yellow tissue, surrounded by narrow zones of hyperemia. No occlusion could be demonstrated in the adjacent vessels. No thrombi were present in the pulmonary veins or heart, and the cardiac septa were intact. Histologic section through the renal lesions showed areas of an advanced coagulation necrosis confined to the cortex and surrounded by narrow zones of hyperemia with a marked polymorphonuclear leukocytic infiltration. The outlines of the tubular epithelial cells and cells of the glomerular tufts were markedly obscured. The nuclei of the parenchymatous and mesenchymal structures were markedly reduced in number, while those remaining were pyknotic or markedly fragmented. In other portions of the cortex were smaller, variably sized, discretely delineated rhomboid shaped areas showing variably advanced degrees of coagulation necrosis. The earliest lesions were manifest only by a loss of the granularity of the cytoplasm of the tubular epithelial cells, which maintained their discrete cell borders, and showed but little loss of nuclei, those remaining being pyknotic. The glomeruli were not affected. In other areas, the process was more advanced, with greater homogenization of a deeply staining tubular epithelial cell cytoplasm, and with blurring of the cell outlines, while their nuclei were more severely diminished in number. Here the outlines of the cells of the glomerular tufts were obscured and their nuclei pyknotic. Although the severity of the change varied from one area to another, the degree of degeneration within any one given area appeared to be uniform throughout that area. Numerous sections throughout the kidney failed to reveal evidence of vascular occlusion, though infrequently nonoccluding finely granular eosinophilic deposits were seen in medium sized and small vessels within the areas of necrosis. The greater portion of the kidney was normal.

The diagnosis was posttraumatic ischemic infarction of the kidney due to arteriospasm.

Case 2.—J. S. S., C. M. H. No. 35849, a 25-year-old white man, was admitted on the neurosurgical service February 6, 1948, four days following an automobile accident. The patient had been unconscious since his injury and expired three hours after admission to the hospital. He showed all the clinical signs of severe intracranial injury and in addition, fractures of several ribs. His blood pressure was 110/80 on admission. A urinalysis was not recorded.

Pathology Report.—Autopsy examination revealed intramuscular hemorrhages of the left posterior abdominal wall and perirenal hemorrhage on this side. There were ischemic infarctions of the spleen and left kidney. There were no sources of emboli in the pulmonary veins or heart and the foramen ovale was closed. The capsule of the left kidney stripped easily, leaving a smooth surface without laceration. There were three closely associated, slightly elevated, yellowish-gray foci of ischemic infarction with surrounding narrow zones of hemorrhage. On section, these lesions were rhomboid-shaped and confined to the cortex. The largest measured 4 cm. in diameter and the smallest 0.5 cm. Within the lesions, the renal architecture was completely obscured. Careful dissection of the vessels failed to reveal occlusions by thrombus. Histological examination of the kidney revealed a variety of changes. The grossly discernible infarcts were areas of complete coagulation necrosis of all elements with a narrow surrounding zone of hemorrhage. There were also several incomplete infarctions which varied from each other considerably. These were discretely delineated from adjacent normal renal parenchyma though not surrounded by zones of hyperemia or leukocytic infiltration. In some of these, the tubular epithelium showed diminution in the numbers of nuclei with pyknosis and karyorrhexis of those remaining, while the glomeruli presented no evidence of necrosis. In other areas, the tubular epithelium showed complete loss of nuclei and marked blurring of cell outlines, while the nuclei of the glomerular tufts were diminished in number with pyknosis and karyorrhexis of those remaining. Regardless of the severity of the glomerular degeneration, numerous small collections of an eosinophilic granular material were encountered within the glomerular capillary lumina in the zones of incomplete infarction, as well as within the otherwise unaltered glomeruli situated in the adjacent entirely viable cortex. Immediately adjacent to one of the areas of infarction, there was a partially organized platelet thrombus in an arcuate artery, but nowhere else was one encountered in numerous blocks studied.

The diagnosis was posttraumatic ischemic infarction of the kidney due to arteriospasm.

Case 3.—P. B., M. G. H. No. 132472, a 42-year-old white man, was admitted on the surgical service on December 21, 1949, shortly after falling 35 feet from a scaffold. He was conscious and complained of chest and back pain. He was described as being in shock and was given a unit of blood plasma following which his blood pressure was 120/68, being recorded for the first time. The abdomen was described as board-like. An x-ray of the chest demonstrated fractures of all the ribs on the right side and of the second and third on the left, all being fractured in the posterior axillary line. The plain x-ray of the abdomen showed fractures of the right transverse processes of all the lumbar vertebrae, fracture of the left pubic bone and a separation of the right sacro-iliac joint. The renal and psoas shadows

could not be visualized. An excretory urogram was not obtained. A retrograde cystogram was made because of the pelvic fractures and was normal. The urine showed 40-50 erythrocytes, 20-30 leukocytes, 2-3 granular casts per high powered field and 3 plus albumin. The patient was treated expectantly and his blood pressure remained at a satisfactory level until he suddenly went into shock and expired 3½ days after admission. The clinical impression was that he had an exsanguinating secondary hemorrhage into the right pleural cavity.

Pathology Report.—There was, in addition to the skeletal fractures noted above, a massive right hemothorax, extensive bilateral retroperitoneal hemorrhage and an area of infarction of the lower pole of the left kidney which measured 3.5 cm. in diameter (*Figs. 1a* and *1b*). This area was a mottled grayish-yellow color and appeared to consist of a conglomeration of coalescing small infarcts. The capsule stripped easily and there was no evidence of laceration of the surface of the kidney. The vascular pedicle was intact and the vessels contained no emboli or thrombi. On section, the area of infarction was found to be sharply confined to the cortex, being rhomboid in configuration. Microscopically, sections through the area of infarction showed the usual picture of necrosis except that there were a number of scattered glomeruli within the area of infarction which were intact, most of these being in the juxtamedullary area (*Fig. 1c*).

Fig. 1(a)

Autopsy specimen from clinical *Case 3* showing posttraumatic ischemic infarction at the lower pole of kidney of 3½ days duration.

The diagnosis was posttraumatic ischemic infarction of the kidney due to arteriospasm.

Case 4.—V. A., surgical pathology No. S-1451-47, a 19-year-old white woman, was admitted on the surgical service at a neighboring hospital on December 5, 1946, shortly after her injury in an automobile accident. She was in mild shock with a blood pressure of 92/60 and a pulse of 110. There was tenderness and rigidity in the left upper quadrant of the abdomen. An urinalysis showed a trace of albumin, a rare pus cell and granular cast, but no erythrocytes. The patient was watched for several hours during which time she received shock therapy. As the abdominal tenderness and rigidity increased, a laparotomy was performed and a ruptured spleen removed. Palpation of the left kidney is said to have revealed no evidence of rupture or of perirenal hematoma; the kidney was not visualized. During the ensuing four months the patient had episodic pain in the left flank associated with several bouts of gross hematuria, and for this reason she was readmitted to the hospital on April 4, 1947. The urinalysis was entirely negative. The flat plate of the abdomen showed a small left renal shadow. Excretory urograms revealed a small narrow pyriform pelvis with well filled superior calyces and an absence of the middle and inferior calyces (*Fig. 2a*). The left kidney was explored and found to be small and densely adherent to the surrounding tissues and a nephrectomy was performed with considerable difficulty. At no time had there been any evidence of pulmonary or cardiac disease which might be a source of emboli.

Pathology Report.—The kidney (*Figs. 2b* and *2c*) weighed 43 grams and measured 7 x 3 x 2 cm. The surface of the lower two-thirds of the kidney was coarsely nodular and retracted. From this portion, the capsule stripped with some difficulty. On section, the cortex and medulla of the upper third were seen to be somewhat, though not markedly, narrowed. The architecture of each in this portion was well preserved, and the corticomedullary junction was fairly discrete. The inferior pole was nearly as well preserved. The intervening markedly retracted portion was roughly rhomboidal in shape with the base at the periphery. The structures within it, for the most part, had lost their normal detail, were largely replaced by homogeneous or trabeculated grayish yellow areas some of which were partially surrounded by narrow zones of hemorrhage. Between these areas were portions in which the architecture, though obscured, was still recognizable. Careful dissection of the renal artery and its branches disclosed no occlusion. Numerous blocks from the retracted area were studied histologically. Large areas of complete coagulation necrosis were irregularly distributed. Within these, the general architecture of the organ was recognizable largely by preservation of thickened basement membranes of tubules, Bowman's capsules and glomerular tufts. The nuclei had disappeared, as had cell outlines such that the tubular epithelial cells formed large deeply staining homogeneous eosinophilic masses. The interstitial elements, as well as the cells of the glomerular tufts, were similarly altered. Within these large areas

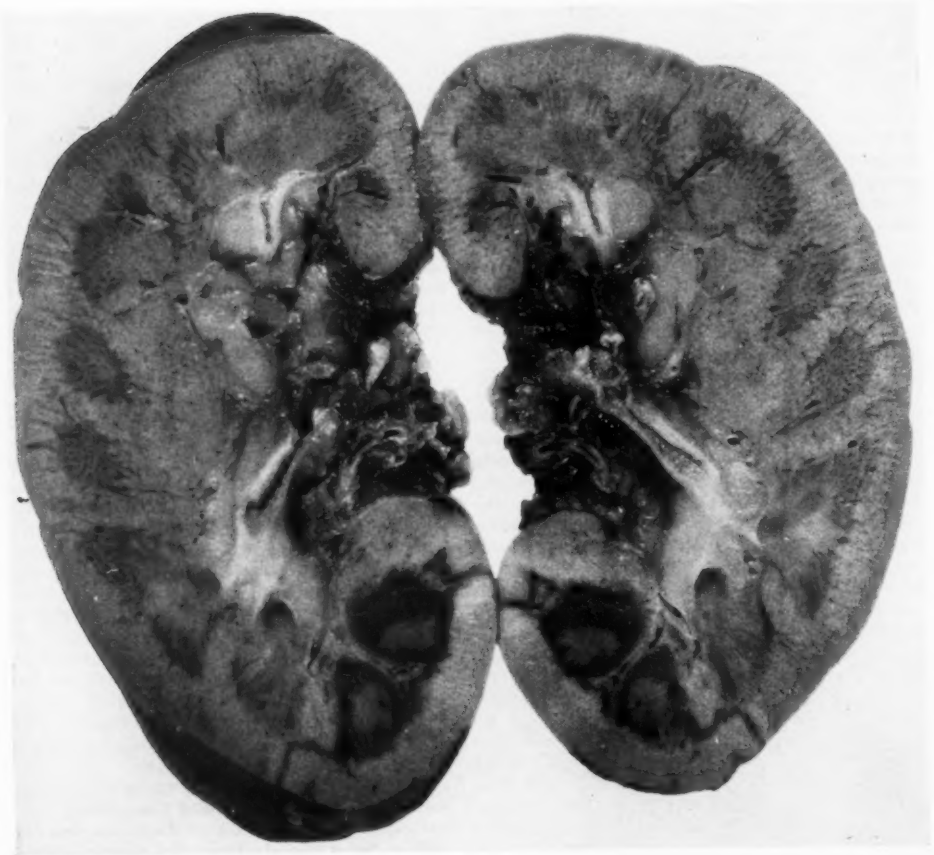

Fig. 1(b)

Midline cut section of same kidney showing the infarction confined to the cortex.

were deposits of hematoidon. Adjacent to these areas were zones of incomplete infarction of tubules and glomeruli. In the less severely involved zones, there was a marked thickening of the basement membranes of tubules and glomeruli and some atrophy of tubular epithelial cells. In further stages, the tubular epithelial cells had lost their nuclei, and were deeply eosinophilic. The glomeruli possessed diminished numbers of nuclei, while those of the interstitium were but little affected. In still further stages, only the connective tissue nuclei persisted. In the most advanced stage, all nuclei had disappeared as described above. Between these various infarctions were areas showing different stages of fibrosis with associated lymphocytic infiltrations. Elsewhere, entirely normal portions of kidney were encountered. Numerous sections failed to show occlusion of vessels, though the lumina of a few of the interlobular arteries were narrowed, the result of hyperplasia of their intimal layers.

The diagnosis was segmental renal atrophy secondary to posttraumatic ischemic infarction of the kidney due to arteriospasm.

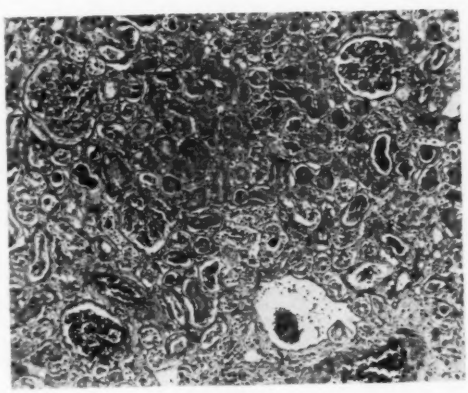

Fig. 1(c)

Photomicrograph (hematoxylin-eosin X 100) of same infarct taken in the juxta-medullary area showing preservation of some glomeruli and tubules.

EXPERIMENTAL STUDY

Material, Methods and Results.—Twenty-two adult 2.7 to 3.9 kilogram rabbits were used in two groups of experiments.

Group 1.—Sixteen rabbits were divided into four subgroups of four animals each and anesthetized for acute experiments using 30 mg. of sodium pentobarbital per kilogram of body weight intravenously as a preliminary dose which was supplemented *ad libitum* as required.

(A) *Effect of Trauma Alone.*—Both kidneys were exposed through a midline abdominal incision and the right kidney was struck with the flat surface of a scalpel handle so as not to cause actual rupture of the kidney.

A transient focal blanching of the organ resulted in the region traumatized, which persisted for 5 to 10 seconds.

(B) *Effect of Tourniquet Plus Trauma.*—A rubber tourniquet was placed about the right lower extremity for a period of four hours following which both kidneys were exposed and the ipsilateral kidney traumatized as in subgroup A.

These animals showed a definite but variable degree of diffuse blanching of the ipsilateral kidney which showed a further transient focal blanching upon being subjected to blunt trauma, but in no case did this focal ischemia persist more than 10 seconds.

Fig. 2(b)

Surgical specimen showing irregular atrophy of the lower two-thirds of the kidney.

Fig. 2(a)

Excretory urogram from clinical *Case 4* taken four months following injury showing absence of the middle and inferior calyces on the left.

Fig. 2(c)

Midline cut section of same kidney showing the preservation of the upper pole and extreme lower pole. Note that the retracted area is made up of a conglomerate of infarcts.

Fig. 3(a)

Rabbit kidney showing small ischemic cortical infarcts induced by experimental trauma.

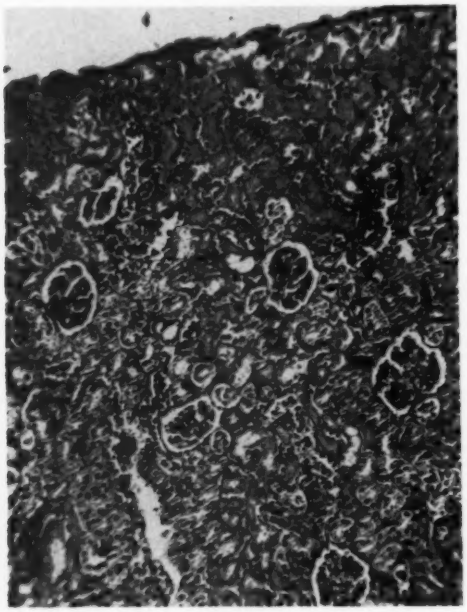

Fig. 3(b)

Photomicrograph (hematoxylin-eosin X 100) through periphery of this lesion.

(C) *Effect of Epinephrine Plus Trauma.*—Both kidneys were exposed and the right kidney traumatized as before as soon as blanching of the organ was noted following the intravenous administration of 0.1 mg. per kilogram of body weight of epinephrine chloride in a 1 to 1,000 solution. This dose was selected as it approximated that used by Trueta *et alii*[21] in their experimental production of renal cortical ischemia in the rabbit.

Shortly after the administration of epinephrine chloride both kidneys blanched from their normal color to a yellowish-brown color which was uniform throughout

Fig. 4(a)

Rabbit kidney showing ischemic cortical infarct induced by injections of epinephrine.

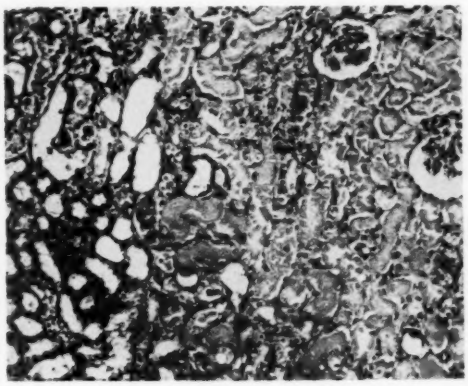

Fig. 4(b)

Photomicrograph (hematoxylin-eosin X 150) of section through the edge of this lesion. Note that the glomeruli are preserved.

the cortical surface. This ischemia persisted for approximately four minutes and was not prolonged by blunt trauma to the kidney during this phase.

(D) *Effect of Tourniquet Plus Epinephrine Plus Trauma.*—A rubber tourniquet was applied to the right lower extremity for four hours following which the kidneys were exposed and the ipsilateral kidney traumatized immediately following the intravenous administration of epinephrine chloride in the same dose as in subgroup C.

As in subgroup B, these animals showed a comparative ischemia of the manipulated kidney which became more marked following the administration of epinephrine chloride but was not prolonged by blunt trauma applied during the phase of marked ischemia.

Group 2.—Six rabbits were manipulated as in *Group 1* and sacrificed at periods varying from 36 hours to 5 days. Of these six animals, three showed significant lesions which are described below.

Rabbit 19.—This 2.7 kilogram animal was anesthetized with sodium pentobarbital and a tourniquet placed about the right lower extremity for four hours. Epinephrine chloride was injected intramuscularly in doses of 0.15 mg. per kilogram of body weight every 30 minutes for eight hours following application of the tourniquet. Thirty minutes after release of the tourniquet, the right kidney was isolated subcutaneously, held in fixed position, and traumatized with the flat surface of heavy surgical scissors. The animal was sacrificed 48 hours later.

Pathological Examination.—Macroscopically, each of the kidneys was normal in size and each was encapsulated. The right kidney possesses an outer surface which is essentially normal with the exception of a small area of subcapsular hemorrhage situated at approximately the mid-portion of the greater curvature, which measures not over 1 cm. in diameter. The borders are irregular. In the vicinity of the hemorrhage there is encountered a pale yellowish gray slightly elevated zone which measures 0.2 cm. in diameter. On section this zone is seen to extend throughout the cortex, being somewhat indiscretely delineated on either side by a narrow zone which is reddish brown in color (*Fig. 3a*). It does not extend into the medulla. At the hilus is attached connective tissue which shows a diffuse interstitial hemorrhage and there are also both artery and vein, each of which is dissected as far as possible, and no occlusion is demonstrated. The opposite kidney is essentially normal.

Microscopically, histologic sections (*Fig. 3b*) through the right kidney in the vicinity of the grossly described subcapsular hemorrhage and pale zone in the cortex, show within the latter variable degrees of degeneration and necrosis of the convoluted tubules and tubuli recti extending through the entire width of the cortex from its surface to the cortico-medullary junction. Small groups of tubules appear to be relatively little, if at all, involved. Many tubules in this area show an eosinophilic homogenization of the cytoplasm, often involving only a portion of the cell, while in some places cellular cytoplasm is completely homogenized. The cell borders are indiscretely delineated and frequently cannot be recognized. The nuclei are markedly diminished in number, and of those remaining many are pyknotic, while others show karyorrhexis. There are a few foci in which the tubular epithelial cell cytoplasm is markedly fragmented, and the irregular fragments possess a peculiar polychromatophilic and somewhat slate gray appearance. These fragments appear to coalesce within the lumen of the tubules. For the most part, a recognizable epithelial lining in such foci has completely disappeared. The glomeruli are intact, as are the vessels, and there is no associated interstitial inflammatory infiltration. Numerous sections through other portions of the kidney show no pathologic changes. In numerous sections no occlusion of vessels is demonstrated. Of importance is the absence of both tubular dilatation and interstitial edema and infiltration which occur in lower nephron nephrosis.

The diagnosis is focal confluent incomplete infarctions involving a portion of the right kidney.

Rabbit 21.—A 3.6 kilogram animal was anesthetized with sodium pentobarbital and the right kidney was isolated, fixed subcutaneously, and traumatized with the flat surface of heavy surgical scissors. The rabbit was sacrificed six days later for study.

Pathological Examination.—The capsule was adherent over the middle third of the right kidney. There were two areas, one on each surface of the kidney, which measured 7 x 5 mm. and 5 x 4 mm., which were slightly depressed below the cortical surface, and which were yellowish gray in color with an irregular narrow surrounding zone of hemorrhage. Cut sections through these areas showed rhomboid-shaped areas of ischemia which were confined to the cortex. Dissection of the arteries failed to demonstrate gross thrombi. Microscopic sections established the lesions as ischemic infarcts. There was no evidence of thrombotic occlusion of the vessels in numerous sections studied.

The diagnosis was posttraumatic ischemic infarcts of the kidney due to arteriospasm.

Rabbit 22.—This 3.2 kilogram animal was anesthetized as in the previous experiments to permit the intramuscular injection of epinephrine chloride in the doses previously used over a period of 8 hours at 30-minute intervals. No trauma was applied. The rabbit was sacrificed at the end of 3 days.

Pathological Examination.—The right kidney was normal in appearance grossly while the left kidney showed a well demarcated roughly circular yellowish white area at the superior pole which was neither raised or depressed below the cortical surface. On section of the kidney the lesion was found to be confined to the cortex (*Fig. 4a*). Microscopic examination showed complete coagulation necrosis of the tubules in this area (*Fig. 4b*). The glomeruli in the peripheral cortex were likewise involved in the necrotic process, whereas many in the juxtamedullary area were spared. There was no peripheral area of hemorrhage nor leukocytic infiltration.

The diagnosis was focal ischemic infarct of the kidney due to arteriospasm.

DISCUSSION

There can be no doubt that injury of the renal pedicle with resultant thrombosis of the renal artery may produce massive infarction of the

kidney. The cases of Barney and Mintz[12] and Hirshberg and Soll[13] are illustrative of this type of traumatic renal infarction. In other cases, such as those of Neuberger,[2] von Marenholtz,[3] Frank and Jaffe,[4] the four clinical cases reported in this paper, and the lesions produced in the experimental animals, we believe that a different physiological and pathological process is involved. Careful examination of these infarcts demonstrated the absence of significant thrombosis of the vessels and we believe that the infarcts were the result of arteriospasm secondary to the trauma.

We are fully cognizant of the objections which might be raised to drawing conclusions from negative findings, to-wit, the failure to demonstrate mechanical occlusion to explain the infarcts. One encounters difficulties in proving the absence of occlusion due to thrombosis or embolus and this is open to skepticism even though serial sections are made. However, our own negative findings are in keeping with those of other authors cited. Moreover, an increasing number of negative observations adds some weight to the assumption that vasospasm may produce infarction of inner organs.

The presence of small thrombi within the confines of some of the infarcts themselves is believed to be the result of the conglutination of erythrocytes and platelets due to stasis.[1 2] This belief is based on our own observations, as well as on the experimental work of Trueta and his associates[21] who described necrosis of the walls of small vessels in ischemic cortical necrosis with usually some sort of thrombus composed of fibrin, platelets, and conglutinated erythrocytes. It is also thought that the incomplete nature of some of these infarcts is further evidence against their causation by thrombotic or embolic phenomena. In the case of Frank and Jaffe,[4] the area of infarction is said to have been confined to the cortex alone and they postulated that this might be due to spasm of the renal artery with stasis in its terminal branches. The recent experimental work of Trueta and his associates[21] on the physiology of the renal circulation has provided experimental evidence along these lines where before there was only conjecture. They were able to produce cortical ischemia while the remainder of the kidney, that is, the medulla and a narrow border of cortex containing the juxtamedullary pathways, remained unchanged. This work would seem to substantiate the possibility of the occurrence of focal renal cortical infarction without thrombosis such as has been described by other authors and by us in this paper.

The evidence would seem to indicate, therefore, that the etiology of the posttraumatic renal infarct may be severe focal arteriospasm resulting from direct trauma to an area of the renal cortex or to stimulation of the splanchnic or renal nerves by the traumatic force. While ischemic infarcts were produced in one animal by trauma alone, it is felt that shock, which was present in varying degrees in many of the clinical cases reported and reviewed, may well be a contributing factor in producing renal ischemia.

CLINICAL CONSIDERATIONS

The clinical picture presented by the posttraumatic ischemic infarct of the kidney does not differ from that of renal infarct due to other causes as described by Regan and Crabtree.[11] Small infarcts may not be demonstrated clinically and will be confused with contusion of the kidney. However, the presence of granular casts in the urine may indicate infarction. Larger infarcts will present absent to diminished function on the affected side and a normal retrograde pyelogram. The contused kidney may have diminished function for as long as several days following injury[23] and infarction should not be diagnosed unless defective function persists beyond this period.

Kidneys with presumptive traumatic contusion should be followed for a period of months to rule out subsequent atrophy and hypertension before the patient is assured that the renal injury has resulted in no permanent damage to the kidney. Although our clinical *Case 4* did not develop hypertension, this sequel to renal infarction has been reported by Arnold, Goodwin and Colston.[24]

Prevention of posttraumatic ischemic infarction of the kidney might possibly be accomplished by splanchnic nerve block on the side of injury if the patient were seen immediately following injury; but as its occurrence seems to be uncommon, this is probably not a feasible routine procedure.

SUMMARY

Evidence is presented to support posttraumatic infarction of the kidney due to arteriospasm as a pathological entity by means of:

(1) A review of the relevant literature.

(2) A presentation of four clinical cases in which the infarcts were 36 hours, 3 days, 4 days, and 4 months old.

(3) An experimental study in which lesions comparable to those in the clinical cases were produced in the rabbit by trauma alone, by injections of epinephrine chloride alone, and by a combination of these agents.

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DISCUSSION (*Abstract*)

Dr. Oscar B. Hunter, Washington, D. C.—It would seem somewhat difficult to explain ischemic infarction on the basis of angiospasm alone, especially when the mechanism of the infarction is said to be specifically related to direct trauma or to stimulation of the splanchnic or renal nerves.

Infarctions in any organ vary naturally in their rapidity and intensity according to the anastomotic or supplementary blood supply.

The kidney is an organ where the terminal arterioles are more or less end arteries and infarctions in an organ of this type would be more rapid and of the anemic type due to the diminished hemorrhage. In most instances an infarct in the kidney is wedge-shaped with the base at the periphery and the apex towards the point of obstruction. Necrosis first affects the parenchymatous elements, and later the supporting connective tissue as well.

It has been shown that ischemic necrosis occurs in the kidney in patients with lupus erythematosus disseminatus, scleroderma, rheumatic fever, periarteritis nodosa, and other diseases. The basic causal factor in all these conditions was related to injury of the renal arteries, thus affording a means of thrombosis or embolism.

Spasm of arteries may occur under various conditions, such as "trench foot," "immersion foot," ergotism and Raynaud's disease. But in these conditions the angiospasm results in injury to the endothelium, dilatation of the capillary bed distal to the spasm and the formation of agglutinative thrombi in the arteries, capillaries and veins. The infarctions in these conditions are the result of a thrombus precipitated by trauma to the vessel walls, and not necessarily a result of angiospasm.

Goodwin, Sloan and Scott have shown that renal ischemia can be produced by peripheral stimulation of renal nerves of rabbits, dogs, cats and monkeys, which demonstrates a neurovascular control of renal circulation. They showed that if the stimulus was of great intensity and duration the kidney might become totally ischemic. Koletsky and Gustafson have demonstrated the effects of temporary cessation of renal blood flow. In their work the principal morphologic change was necrosis of the descending segment of the proximal convoluted tubules. In these instances the resulting pathologic changes were confined to a part of the nephron similar to that observed in the crush syndrome. Involvement of a whole segment or part of the kidney was lacking.

It would seem that in the results of Drs. Large and Lynch the blanching effects in the kidneys traumatized occurred as a result of temporary focal cessation of renal flow. If the vessel walls had been injured, focal ischemic necrosis would have ensued. Trauma, *per se*, could be the etiologic factor of the infarction provided it was of sufficient intensity. In this instance, however, the resulting necrosis could be explained on the basis of localized tissue metabolism with changes in the hydrogen ion concentration and cytologic dissolution. With the use of epinephrine chloride and trauma the resulting infarction could be explained more appropriately on the basis of tissue destruction by a chemical.

There is no question that angiospasm in the kidney, associated with trauma of sufficient intensity can result in ischemic infarction whether it be precipitated by a vasoconstrictor, or nerve stimulation. It would seem to me, however, that these mechanisms would not be sufficient to produce ischemic infarction without adequate arterial damage necessary for the formation of a thrombus or embolus.

Dr. J. F. A. McManus, Charlottesville, Va.—Angiospasm is probably as good an explanation for this type of lesion as we have. Dr. Hunter questioned whether this lesion occurs in the so-called "crush" kidney. I have seen one such case in war injuries and we were unable to find any source of embolism of which we could be sure.

The infarction, as Dr. Lynch and Dr. Large showed rather beautifully, is restricted to the outer two-thirds and three-quarters of the cortex. Now, that is the level at which the arteries of the kidney take on a muscular character as opposed to the mixed elastica type which you see in the larger arteries. That is the point at which the arteries became fixed within the kidney substance. They are traveling in fat and loose connective tissue before that point, where the so-called arcuate arteries

give over to the muscular interlobular arteries. These would be the arteries where spasm would be most severely felt. The occasional occurrence of this infarction in the "crush" lesion still leaves us wondering why we do not see it more frequently. But that along with other problems of the "crush" lesion will I am sure be further studied.

Dr. Lynch (closing).—I particularly wish to acknowledge that Dr. Hamilton McKay initially stimulated my interest in the injured kidney several years ago, and that the work that we are reporting is a direct result of that interest. I neglected to emphasize the fact that all of our clinical cases were in shock of varying degrees of severity and duration, and that we believe that this is a contributing factor in the production of these infarcts. Various authors who have reported on cortical necrosis of the kidney in cases of shock have postulated that the arteriospasm is due to a toxin liberated from an injured liver. We ligated the liver *en masse* in a few rats, but found no changes in the kidneys when the animals were sacrificed several days later. Time prevented our discussion of Dr. Willard Goodwin's work on the Trueta phenomenon which Dr. Hunter has mentioned. Although this has not been published, Dr. Goodwin did get actual infarction of the kidney in some of the animals in which the renal nerve was selectively stimulated.

Dr. Large (closing).—Dr. Hunter, since we excluded endothelial proliferation, I take it you were inquiring about damage to individual endothelial cells. Undoubtedly there is what is being called "endothelial swelling" in small vessels, but we are at a loss to evaluate it.

We should like to emphasize a repeatedly made fundamental observation upon which, by inference, our conclusions are partially drawn, namely: in injuries to extremities and in particular penetrating wounds, the orthopedic and general surgeon has observed at open surgery a small segment of an artery to be constricted, as they say, "to the size of a knitting needle."

A CLINICAL EVALUATION OF ANTACID THERAPY IN THE TREATMENT OF THE PEPTIC ULCER SYNDROME*

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Although the exact roles of hydrochloric acid and gastric pepsin in the production of the peptic ulcer syndrome are not in all respects entirely obvious, there is a large body of experimental observations which indicates that the partial neutralization of this acid and the maintenance of a hydrogen ion concentration sufficiently low to inhibit peptic activity is a desirable therapeutic aim during the acute stage of this disease. We believe that dietary measures alone will not accomplish this in most cases, and the administration of some form of alkali will be necessary. These views are held because of observations we have made on various patients using single test meals of milk and cream, in the same proportions as are given in our standard ulcer diet regime, and observing the hydrogen ion concentration and free and total acid levels of specimens aspirated from the stomach at intervals over a period of two to three hours.

From *Table 1* it may be seen that after a single dose of 100 cc. of a mixture of whole milk and cream, the *p*H remained above the desired level in most of these subjects for a period of one

SUBJECTS AND *p*H

Hydrogen ion values of gastric aspirates from 8 subjects following the single ingestion of 100 cc. of a milk and cream mixture.

	D.J.	P.B.	V.S.	L.C.	C.L.	A.S.	G.C.	W.W.
Time Minutes Fasting	6	2	4	1	4	6	4	6
Milk and cream 100 cc.								
15°	5.5	4.5	6	6	4.5	5	5.5	6
30°	5.5	3	6	6	4.5	4.5	4	4
60°	4.5	2	5	4.5	4	4.5	2	4
90°	4	1.5	5	3	1.3	2	1	2
120°	2	1.5	4.5	1.5	1	2	1	2
180°		1.5	3.5	1.5	1	2	1	2

Table 1

SUBJECTS AND *p*H

Hydrogen ion values of gastric aspirates from 7 subjects following the single ingestion of a 100 cc. mixture of 15 grams of a protein digest in water. The *p*H in this experiment fell after the first hour in a manner comparable to the fall exhibited in *Table 1.*

	D.J.	V.S.	L.C.	C.L.	A.S.	G.C.	W.W.
Time Minutes Fasting	4.5	4	2	1.5	6	2	6
15 grams of protein digest mixture in 100 cc. water							
15°	6	6	6	5	6	5	5
30°	6	5	4.5	4	6	4.5	3
60°	4	4.5	4	2	6	4	2
90°	2	4.5	2	1.5	4	1	2
120°	2	4.5	1.5	1	2	1	2
180°		4	1	1		1	

Table 2

*Read in Section on Gastroenterology, Southern Medical Association, Forty-Fourth Annual Meeting, St. Louis, Missouri, November 13-16, 1950.

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hour, but acidity of a degree sufficient to stimulate peptic activity returned promptly in each after that period of time. These subjects had been previously tested by alcohol test meals and were known to be able to secrete acid in a concentration sufficient to produce a *p*H of 2 or below. Seven of the eight same subjects were likewise given test meals containing 15 grams of 2 different types of protein digests suspended in 100 cc. of water. Neither of these preparations showed any neutralizing properties superior to those obtained with the milk and cream mixture as is shown by comparison of the figures in *Tables 1* and *2*. After the first hour the *p*H was below 4.0 in both types of experiments in the majority of the subjects, the only exception being V. S. in both experiments.

When multiple test meals of milk and cream were given every hour and aspirations continued at intervals over a period of 3 hours, to our surprise, the *p*H continued downward to more acid levels after the first hour in the same fashion as was observed to occur with the single test meal of milk and cream (*Tables 4* and *5*), thus indicating in some patients that hourly feedings of milk and cream mixtures result in no additional neutralizing effects after the first hour, and that the local neutralizing effect is entirely counterbalanced by the phase of intestinal secretion. I must stress the words "some patients" at this point because the number of patients tested by this technic is as yet not extensive enough to be sure that this is to be expected in all instances. It has been true in all of the twelve peptic ulcer patients who have to date been tested by this method. Neither banthine® in 100 mg. doses given 1 hour prior to the first test meal nor atropine in 0.6 mg. doses given by hypodermic at the time of the first test meal has been observed to have any inhibiting effects in decreasing the lowering of *p*H when this type of test was performed in 3 subjects. No *p*H lowering was observed by either of these drugs in repeated alcohol test meal experiments in 7 subjects. We have as yet not extended any of our observations to periods of more than 4 hours, but such a study is now in progress.

With this background of observations it was deemed desirable to test a number of subjects with such test meals as had been previously utilized and add to these antacid preparations to observe whether more adequate *p*H control could be observed by this means when the antacids were employed. The dosages used were of the same order as those ordinarily used on our service; these being doses which clinically seemed adequate from the standpoint of giving symptomatic relief in the majority of our patients. These observations are contained in *Tables 3* and *5*.

From these figures, as might be predicted, it is evident that the degree of the acidity is appreciably reduced by antacids for periods of 30 to 60 minutes in patients who by alcohol test meals can be shown to maintain a strongly acid *p*H for 2 hours after a single test meal of 100 cc. of 7 per cent alcohol. The first line of figures for each subject are the results in that patient as observed after an alcohol test meal

TIME AND *p*H

Buffering effect of 1 gram of each of 2 types of antacids after gastric stimulation by an alcohol test meal in 3 subjects.

Subject	Fasting	15°	30°	60°	90°	120°	Alcohol test meal
I. M.	5	1	1	1	1.5	1.5	
I. M.	6	1.5	1.5	6	3	1.5	Alcohol test meal and magnesium trisilicate given at 35 minutes
C. C.	4.5	3	2	1.5	1.5	1.5	Alcohol test meal
C. C.	1.5	1	1	4.5	4	5	Alcohol test meal and magnesium trisilicate 1 gram at 35 minutes
C. C.	6	4	1.5	5	1.5	2	Alcohol test meal and 1 gram resin at 35 minutes
L. C.	2	1	1	1		1	Alcohol test meal
L. C.	1	1	1	4	1.5	1	Alcohol test meal and 1 gram magnesium trisilicate at 35 minutes
L. C.	1.5	1	1	6	5	2	Alcohol test meal and 1 gram resin at 35 minutes

Table 3

Hydrogen ion concentration of gastric aspirates from a subject given hourly feedings of milk and cream plus 1 gram of an ion exchange resin at the first and third feeding.

Fasting	Milk and cream plus 1 gram resin	60 min.	Milk and cream alone	120 min.	Milk and cream plus 1 gram resin	180 min.
7.0		5.6		1.8		5.3

Table 5

A summary of the response shown by patients with peptic ulcer on the same treatment regime but with 3 different forms of antacid preparations.

Total Number of Patients, 100		Hospital Treated, 57	Outpatient Treated, 43
Diagnoses:			
Duodenal ulcer	83	41	42
Gastric ulcer	13	12	1
Gastric and duodenal ulcer	3	3	0
Marginal ulcer	1	1	0
Average duration symptoms prior to treatment	49.7 days	44.2 days	57 days
Average duration symptoms after starting treatment	19.4 days	12.4 days	28.6 days
Maximum		75 days	185 days
Minimum		1 day	2 days
Number patients treated with resin	33	15	18
Average duration symptoms prior to treatment	55.6 days	60.1 days	68.7 days
Average duration symptoms after starting treatment	14.8 days	9.1 days	20.0 days
Per cent symptom free in 3 weeks or less	85.0	93.3	72.2
Number patients treated with magnesium trisilicate	23	13	10
Average duration symptoms prior to treatment	62.5 days	59.3 days	66.6 days
Average duration symptoms after starting treatment	13.4 days	14.9 days	11.4 days
Per cent symptom free in 3 weeks or less	87	84	90
Number patients treated with aluminum hydroxide	44	29	15
Average duration symptoms prior to treatment	38.5 days	39.2 days	36.5 days
Average duration symptoms after starting treatment	25.9 days	13.0 days	50.7 days
Per cent symptom free in 3 weeks or less	75.0	93.1	33.3

Table 6

Cumulative per cent of patients well by weeks calculated from the number from each group symptom free by weeks.

Antacid	Hospital Cases Weeks				Outpatient Cases Weeks			
	First	Second	Third	Fourth Plus	First	Second	Third	Fourth Plus
Resin								
Total 33								
Hosp. 15	46.6 per cent	86.6 per cent	93.3 per cent		22.2 per cent	55.5 per cent	72.2 per cent	
OPD 18								
Actual number cases symptom free	7	6	1	1	4	6	3	5
Magnesium trisilicate								
Total 23								
Hosp. 13	23.7 per cent	61.5 per cent	84.6 per cent		60 per cent	70 per cent	90 per cent	
OPD 10								
Actual number cases symptom free	3	5	3	2	6	1	2	1
Aluminum hydroxide								
Total 44								
Hosp. 29	51.7 per cent	79.3 per cent	93.1 per cent		0 per cent	20 per cent	33.3 per cent	
OPD 15								
Actual number cases symptom free	15	8	4	2	0	3	2	10

Table 7

Results of follow-up x-ray studies.

	X-rayed	Not X-rayed	Healed Seven Weeks or Less		No Change	
			No.	Per Cent	No.	Per Cent
Resin	15	18	15	100	0	00
ALOH	25	19	22	88	3	12
Mag. Tri.	10	13	9	90	1	10
Total	50	50	46	92	4	8

Table 8

more ideally treated hospital cases this difference was not so evident (*Table 7*). Other factors such as the lack of constipating effect and the lack of any small intestinal irritation are qualities which may cause one to prefer the ion exchange resin over the other 2 alkalis studied, but these considerations will vary from case to case for various reasons. In this study 8 cases could not be included because of the need for changing the form of alkali used because of various difficulties experienced by the patients from its use. This occurred 5 times with the ion exchange resin and 3 times with the other antacids.

SUMMARY

(1) Experimental data are presented which indicate that milk and cream feedings alone will not neutralize the gastric contents sufficiently to inactivate pepsin. Some form of alkali is needed in addition.

(2) Clinical observations as to the effectiveness of 3 types of antacid preparations in a group of 100 peptic ulcer patients have been reported; 57 of these were treated in the hospital and 43 in the outpatient clinic.

(3) In the group of patients handled in the outpatient clinic magnesium trisilicate and an ion exchange resin appeared to be superior to aluminum hydroxide.

(4) In the more ideal situation, namely, with the patient at rest in the hospital during the first month of treatment, no significant differences were observed between the rapidity of symptomatic relief in any of the three groups of patients receiving these antacids.

(5) With x-ray study comparable numbers of patients treated with the 3 types of antacids showed x-ray healing in 7 weeks or less on follow-up examinations.

DISCUSSION (*Abstract*)

Dr. Donald F. Marion, Miami, Fla.—A few years ago Dr. Kenamore offered convincing evidence to demonstrate the effectiveness of mixtures of milk, cream, and protein hydrolysates in acid neutralization. The controversy over the merits of intact versus predigested protein seems ended with rather conclusive proof of the superiority of the latter by Dr. Kenamore, Dr. Jerome Levy, Dr. Moseley's group, and others.

Complete 24-hour acid neutralization has never been our objective nor is it required to permit satisfactory healing of peptic ulceration. Dependable measures to raise *p*H to well above the still unknown critical level, however, must be found. Most gastro-enterologists find the present palatable hydrolysates a very helpful supplement to the other measures long in use. I doubt that many of us are willing to dispense with aluminum hydroxides, magnesium trisilicate, or one of the polyamine resins, however, in the management of most of our ulcer patients.

Dr. Jerome S. Levy, Little Rock, Ark.—Drs. Moseley and Coker have re-emphasized the general conception of the need and the extent of buffering of gastric acidity in the management of peptic ulcers. In 1940, Kirsner and Palmer demonstrated that a mixture of milk and cream failed to raise gastric *p*H to antacid levels. This has been confirmed by others and again by Dr. Moseley. This is in accordance with my own observations.

However, my own experience is not in agreement with his conclusions on the buffering capacity of the protein hydrolysates. Previous studies which I have reported at the American Gastro-Enterological Association meetings have shown that a 10 per cent solution of protolysate, a protein hydrolysate, buffers gastric acidity for longer periods than does milk and cream, and, when given hourly in solution in milk and cream instead of water, completely buffers gastric acidity throughout the day.

Referring to his charts, it will be noted that Dr. Moseley demonstrated both the milk-cream mixture and the hydrolysates buffered well for an hour, and that the *p*H fell appreciably from then on. This is to be expected as 100 cc. of either would have been emptied from the stomach in an hour's time and if not present in the stomach could not be expected to buffer the contents. This does not negate their use when given in hourly feedings. My own studies have shown that the hydrolysates are superior to milk and cream alone, but when given in combination the latter surpasses either alone.

Further reference to *Table 3* shows that Dr. Moseley has not demonstrated any marked superiority of the antacid given at the 35-minute period after an alcohol test meal. The 90-minute specimen may be compared to the 60-minute specimen in *Tables 1* and *3*, and there is not any significant difference. However, this does not negate his findings either. It but adds emphasis to his observation that clinical response has been and is being obtained by the use of these antacids, even though they are not the perfect buffers they are advertised to be! The results he reports are in accord with the experi-

ence of all of us and point clearly to the clinical response obtained without full neutralization. My experience with the protein hydrolysates convinces me that they are of great value in treating the complicated ulcer such as the chronic recurrent, obstructed, or bleeding one. Adequate buffering to a *p*H of 4.0 or above can be maintained throughout the day and the patient be given a high protein intake at the same time. Where the latter is not too important, the chemical antacids are very satisfactory adjuncts as Dr. Moseley has shown.

RINGWORM OF THE SCALP: TREATMENT WITH TETRACHLORO-PARA-BENZOQUINONE*

CLINICAL AND LABORATORY ANALYSIS

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Sixteen hundred and seventy-seven A.D. marked the beginning of the study of fungi. Hook was interested primarily in fungi that affected plants and in particular those which affected rose leaves.

Centuries later, after libraries of information have been gathered concerning fungi as they affect animals as well as plants, their characteristics, mode of infection, physical and chemical characteristics, signs and symptoms of infection and cure, we have the temerity to discuss further topical treatment of ringworm in the scalp.

An Atlanta physician with an avocation of raising orchids first brought to our attention the known bacteriocidal and fungicidal properties of spergon®[1] as applied to horticulture. This marked the beginning of our interest in spergon® as a fungicidal agent in superficial pathogenic dermatomycoses.[2,3]

METHODS, MATERIALS, AND TECHNICS

One hundred eighty-three patients with tinea capitis were studied for a period of one year, beginning August 1, 1949. These cases were observed in private practice and through the health department of the City of Atlanta, which conducted a survey of the Atlanta public school system for ringworm of the scalp. The children ranged in age from 14 months to 13 years with an average age of 7.1 years; there were 153 males and 30 females in the group. The disease in these patients had been known to be present from 1 week to 3 years, and in many of the cases the first knowledge of the presence of the disease was discovered by the visiting nurse. Twenty-eight of these patients had been treated with other medication for periods varying from 1 to 30 months without visible change. The remaining number began their treatment with and have continued to use tetrachloro-para-benzoquinone as a local application.

Spergon® used in this investigation is a yellow powder, contains 96 per cent tetrachloro-para-benzoquinone with 4 per cent inert ingredients. Tetrachloro-para-benzoquinone was incorporated in concentrations, ranging from 3 to 40 per cent in various ointment bases. The two most satisfactory bases were of the water miscible type.

(1)	Glycostearin	20.0
	Glycerin	15.0
	Cetyl alcohol	2.0
	Carbitol	5.0
	Water	58.0
		100.0
(2)	Carbowax 1500®	q. s.

Parents were instructed to clip or shave the entire scalp, once each week. Instructions were given as to a daily shampoo and thorough application of the local medication. Observation at weekly intervals was requested.

All patients were examined first by means of filtered ultraviolet rays (Wood's light). Suspected areas were cultured by aseptic technic, and the fungi were grown on Sabouraud's media at room temperature. Only cases with positive cultures were included in this series. All visits were closely followed by observation with the aid of a Wood's light.

The experimental studies with spergon® were carried out on six known strains of organisms:

(1) Microsporon audouini
(2) Microsporon canis
(3) Tricophyton gypseum

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*Read in Section on Dermatology and Syphilology, Southern Medical Association, Forty-Fourth Annual Meeting, St. Louis, Missouri, November 13-16, 1950.

*From the Department of Medicine, Section of Dermatology, Emory University School of Medicine, Atlanta.

*The tetrachloro-para-benzoquinone used in these investigations was supplied through the courtesy of the United States Rubber Company, Naugatuck Division, New York, under the name of spergon.®

*The authors are grateful to the United States Public Health Service, Communicable Disease Center, Mycology Unit, Atlanta, Georgia, and especially indebted to Dr. Libero Ajello and Dr. Morris Gordon for the laboratory work.

*The authors would like to express appreciation to the Health Department of the City of Atlanta, Dr. J. F. Hackney and his aides for their interest in this work and for the use of their facilities.

(4) Tricophyton mentagrophytes
(5) Tricophyton rubrum
(6) Epidermophyton floccosum

Autoclaved Sabouraud's broth was selected as the culture medium for these studies.

Tetrachloro-para-benzoquinone (spergon®) in quantities from 1 to 100 mg., was incorporated in 25 cc. of the culture medium in a series of flasks, one group of flasks for each organism to be tested. The cultures were incubated at 25° C. (room temperature). Daily observations were made as to the presence or absence of growth. In order to determine the effect of spergon® on the acidity of the solution a careful check of the *p*H was made of the various concentrations of the tetrachloro-para-benzoquinone in the media.

RESULTS

(1) *In Vitro.*—Six known, standard strains of pathogenic fungi, as listed above were tested for growth in autoclaved Sabouraud's broth with serial dilution of tetrachloro-para-benzoquinone. It was found that 0.04 per cent solution (10 mg. per 25 cc.) stopped growth of all tested organisms.

Organism	Control	Spergon® Concentration				
		0.004 Per Cent	0.02 Per Cent	0.04 Per Cent	0.1 Per Cent	0.4 Per Cent
M. audouini	+	+	+	0	0	0
M. canis	+	+	0	0	0	0
T. gypseum	+	+	+	0	0	0
T. mentagrophytes	+	+	+	0	0	0
T. rubrum	+	+	0	0	0	0
E. floccosum	+	+	0	0	0	0

It was found that the greater the concentration of spergon® the lower the *p*H of the resultant solution, to-wit:

Control	6.6
1 mg. in 25 cc.	6.4
5 mg. in 25 cc.	6.05
10 mg. in 25 cc.	5.5
25 mg. in 25 cc.	5.0
100 mg. in 25 cc.	4.6

Dermatophytes grow well at a *p*H of 5.5. Therefore the *p*H did not influence the fungicidal properties of tetrachloro-para-benzoquinone in a concentration found to be destructive to the tested pathogens.[2,3] Tests with solid media confirmed the findings indicated above for liquid media.

(2) *In Vivo.*—Positive cultures with identification of the offending organism were required for inclusion in this series of 183 patients with clinical tinea capitis. Filtered ultraviolet light (Wood's light) facilitated the finding of cases and in following the clinical course. In 16 cases the pathogen was found to be Microsporon canis. Two cases, brothers, were found to have a mixed infection of Microsporon canis and Microsporon audouini. The remainder, 165, were found to be due to Microsporon audouini.

Criterion of cure was absence of fluorescence for 2 months after treatment was discontinued. A patient was classified as improved if there was less fluorescence in a period of 8 weeks. Unimproved cases were so classified when no substantial change in fluorescence was discernible in 8 weeks.

One hundred thirty-one patients were treated with a 3 per cent concentration of tetrachloro-para-benzoquinone in equal parts of cold cream and petrolatum. Of this group 37 (13, M. canis; 24, M. audouini) patients or 28 per cent were cured. Sixty-nine or 52 per cent were improved. Twenty-five or 19 per cent were unimproved.

Twenty-two cases of tinea capitis as seen in private practice were placed on a preparation containing 20 per cent concentration of tetrachloro-para-benzoquinone in a water miscible ointment base as described previously. Of this group 11 or 50 per cent were cured, 8 or 36 per cent were improved, and 3 or 13 per cent were unimproved.

A series of 30 patients obtained from private practice were treated with a 40 per cent concentration of tetrachloro-para-benzoquinone in a base of carbowax 1500®. Of these, 20 or 70 per cent were cured, 6 or 20 per cent were improved, and 3 or 10 per cent were unimproved. It is interesting to note that 3 patients of this series developed a true kerion. Four others developed a mild inflammatory reaction while under treatment. The inflammation was not severe enough to require discontinuation of treatment. In no other concentration was inflammation encountered. There was no evidence of generalized toxicity.

We found that duration of the infection and treatment with other preparations previously, bore no relation and could not be correlated with the response of patients to topical applications of tetrachloro-para-benzoquinone. Size of the areas of involvement with ringworm were of relative unimportance other than the ease of caring for a smaller area.

DISCUSSION

Tetrachloro-para-benzoquinone has been found by other investigators to be nontoxic when applied to human skin in ointment form.[3]

We have found this material to be an excellent fungicidal agent by *in vitro* and *in vivo* experiments. In the foregoing series of cases of tinea capitis a cure was effected in 28 per cent of patients on which a 3 per cent concentration of spergon® was used in an ointment base; 50 per cent when 20 per cent concentration was used in a water miscible base; and 70 per cent when 40 per cent concentration was used in carbowax 1500®.

It is the opinion of the observers of the clinical course of these patients that parental interest and energy are of prime importance in effecting a cure of this condition. Economic status of the family all too frequently influences the rate of cure of tinea capitis since working mothers have less time adequately and properly to care for their children both in health and in the presence of disease. In other words, any treatment is only as effective as the efficiency with which it is used. We believe that tetrachloro-para-benzoquinone is a valuable agent in combating the extremely resistant disease entity known as tinea capitis.

CONCLUSIONS

(1) *In vitro* experiments show tetrachloro-para-benzoquinone to be an active fungicidal agent in as low concentration as 0.04 per cent.

(2) Experiments *in vivo* show this chemical to be active in low concentrations but considerably more effective when the concentration is raised to 20 to 40 per cent and incorporated in a water miscible base.

(3) The economic level of the patient's family frequently has a direct bearing on the efficient use of medication and subsequent cure of patients suffering from tinea capitis.

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DISCUSSION (*Abstract*)

Dr. Ray O. Noojin, Birmingham, Ala.—Dr. Rankin and his colleagues have presented the results of a worthwhile study. Tinea capitis, due to Microsporon audouini, is frequently seen in certain areas; and its chronic and therapeutically-resistant course usually demands a prolonged period of therapy. By means of roentgen epilation, which hitherto has been the most widely advocated form of treatment, nine weeks or more are usually required for a cure. In addition, the use of x-ray therapy necessitates a skillful technic and involves certain dangers. The authors, in prescribing various strengths of spergon® in water miscible ointments, have achieved favorable results when concentrations of 20 to 40 per cent of the drug were used. In view of the difficulties encountered in persuading certain patients to cut or shave their hair frequently and to apply an ointment daily for an indefinite period, it would be of interest to know how long it took the majority of these patients to obtain a cure.

In May, 1946 Collins and his gro.. in the *Urologic and Cutaneous Review*, reported the results of a similar investigation utilizing local spergon® therapy in treating tinea capitis. Microsporon audouini infections were found to respond as readily as those due to Microsporon felineum and members of the trichophyton group. In a group treated with 2.5 per cent spergon® ointment, 38 per cent were cured in an average period of eight weeks or less. This treatment compares favorably with that noted with the use of roentgen epilation.

McGavack and his group in the *Archives of Dermatology and Syphilology*, January, 1950 and Sompayrac (The Schoch Letter, November, 1950) have also confirmed the more favorable results obtained when 30 per cent or stronger spergon® concentrations were used.

This discussant has on two occasions recovered by culture Microsporon audouini from the scalps of spergon®-treated children said to have shown no fluorescence under the Wood's light more than one month previously. These may have been reinfections. On the other hand strong spergon® ointments tend to reduce fluorescence rather rapidly. In order to prevent premature cessation of therapy, do the authors feel that a negative fluorescence for a two months period is adequate? Should a negative microscopic preparation and culture be required?

The experimental work of McGavack and his group in the March, 1943 *Journal of Industrial Hygiene and Toxicology*, and Reque (personal communication) indicate a low toxicity, for spergon.® This fact plus its apparent therapeutic effectiveness should justify more extensive investigation and clinical trial.

Dr. Irving D. London, Montgomery, Ala.—Shortly following the first announcement by the authors of this paper of the use of spergon® at the September, 1949 meeting of the Southeastern Dermatological Association, we treated twenty-four colored children at the John Andrew Clinic of the Tuskegee Institute with three per cent spergon® for tinea capitis. All of these cases were of Microsporon audouini type. Within several weeks, we noted in a few children that the hairs in the involved areas became less fluorescent, or non-fluorescent, entirely,

However, on pulling some of the hairs, fluorescence of the root of the hair was noted, and a potassium hydroxide mounting showed the root of the hair to be infected with spores, although the upper part of the hair appeared to be fairly free.

I might digress here for a moment and mention another method of therapy that we tried on these children. We used an old remedy that was recommended in a small town nearby, copperas in cider vinegar. We found the same results, namely, there was less fluorescence. On pulling the roots of the hair, we could see spores around the hair sheath on microscopic examination.

Our first results with the use of the 3 per cent spergon® in equal parts of cold cream and petrolatum yielded only three cures in 24 cases, within a period of two to three months. These occurred in children who had only one single area infected with the fungus. At a later date, 20 per cent spergon® in the same base was used on the remaining cases. Only one additional cure resulted in this group within a three-month period. I believe that our failures in treatment at Tuskegee were due to the fact that we were dealing with colored children of a low economic level. We did not see most of the parents of these children, and directions for treatment were given to the parents by the school teachers. I, therefore, agree with Dr. Rankin's statement that the economic level of the patient's family had a direct bearing on the efficacy of treatment of ringworm of the scalp.

I have used 6 to 20 per cent spergon® in ointment or in powder for ringworm of the feet, groins and the glabrous skin. Some of these have improved in a very short time, and it has been possible to control a widespread tinea corporis of the tinea purpureum type with spergon® in a matter of several months. I said, "control" because this patient was not cured.

I should like to ask Dr. Rankin whether he believes the higher percentage of cures in his series using the higher concentrations of spergon® is due to the penetration of the hair follicle with the emulsion type of base.

In conclusion, in spergon,® we have another fungicidal agent, probably as good, if not better than any topical agent we have had for the treatment of tinea corporis. This must be used in proper concentration and the proper vehicle, preferably a water soluble base, and with proper attention to detail of shaving the scalp weekly and rubbing the ointment in thoroughly daily.

Dr. James G. Thompson, Jackson, Miss.—I have treated 65 cases of ringworm of the scalp with spergon.® Previously I had been treating ringworm of the scalp with various and sundry things, one was mercury and iodine, which caused a lot of irritation, but seemed to cure some of them. The other one was 5 per cent salicylanilid which seemed to cure some of them, but not all of them.

At the Southeastern Dermatological Association meeting in September, 1949, I learned of the usefulness of spergon.® I immediately wrote the United States Rubber Company for it.

The previous speaker mentioned having trouble with the lower economic group. My trouble was with the higher economic group in that they did not wish to cut their children's hair. In fact, some of them absolutely refused to cut it. I proceeded to treat these children without cutting the hair. Dr. George Lewis cultured some of the hair. The greater number were proved to be Microsporon lanosum. The patients who cut their hair and washed the scalp thoroughly, massaging it with the fingers and removing all of the debris possible by that method, got along exceedingly well. I considered them cured when they did not have fluorescent hairs, or fluorescent root hairs at the end of a month. Now, it may be some of them relapsed, but my impression is, and I do not have the figures on the absolute cures, that this has been an excellent remedy in my hands, and I feel that more of the children would have been cured if I could have persuaded the parents to cut the children's hair.

Dr. Robert C. Thompson, Charlottesville, Va.—I should like to ask the speaker two questions. First, I understood him to say that the drug was non-toxic. I assume that he means the drug is not absorbed, but I am wondering if it is irritating to the scalp.

Dr. Jack Young, working in our clinic with another drug last year, and working only with patients with Microsporon audouini infection, was able to cure a considerable number of them, primarily I think, because his drug was somewhat irritating and caused an inflammatory reaction of the scalp. Furthermore, the patients usually developed a positive tricophyton skin test. I should like to ask Dr. Rankin if any of these children were followed with the tricophyton reaction.

Drs. Livingood and Pillsbury, several years ago, in the *Journal of Investigative Dermatology,* showed that they could cure a good many of these children with Microsporon audouini infection of the scalp, if they could simply get a good inflammatory reaction started, even though they used a drug that was not particularly fungicidal.

Dr. Everett R. Seale, Houston, Tex.—It is difficult for me to understand how a fungicide applied to the scalp can get into the hair follicle and cure ringworm of the scalp. As I see it cure results when infected hairs are removed from the scalp and this may be accomplished by manual epilation, x-ray epilation, from the result of inflammation of the follicle or by the irritative effect of an ointment base which gets into the follicles. If a carbowax® base is used on the scalp after it has been epilated with x-ray, and the scalp is then examined under a Wood's light, plugging of the follicles will be noted. It is difficult to evaluate the value of any fungicide since excellent results have been reported from the use of the carbowax® ointment base alone.

Dr. Morris Moore, St. Louis, Mo.—There are a few points that I should like to bring out. In the first place, the *in vitro* tests for many of the fungicides have very little significance simply because most of them will work well in the test tube and yet seem to have little practical value when applied to the scalp.

The second point I had in mind, what Dr. Seale has just pointed out, pertains to penetration into the hair follicle. Penetration has been one of our greatest problems in the treatment of tinea capitis. Several years ago when Sulzberger and his group came out with their

intraderm® I immediately made use of that, combined with various fungicides, and had it tried in our clinic. It seemed to work quite well except that it produced too much inflammation. Inflammation is said to be very helpful in the treatment of tinea capitis. It is to some extent, except in those cases where the inflammation is so great that treatment has to be stopped.

There is one other point. We have found in our clinic that the best treatment for tinea capitis, especially that caused by Microsporum audouini, is for the patient to develop mumps. We have had several patients who after a course of mumps all came back absolutely cured of ringworm of the scalp.

Dr. Emmett R. Hall, Memphis, Tenn.—I have been very much interested in the treatment of ringworm of the scalp because I have seen an unusually large number of cases during the past year.

My first introduction to the use of spergon,® manufactured by the United States Rubber Company, was in September a year ago, at Atlanta. Since that time, I have used it a number of times and was favorably impressed. I cannot say that it is outstanding, but I can say that it has proved as valuable, or more so, than any of the other agents I have previously used. I am still of the opinion that the nursing care and in some cases, manual epilation or epilation by x-ray, is absolutely necessary for a quick and permament recovery.

I note that most of the speakers today report no systemic reaction to the use of the drug. I had a case, a child of 8 years of age, using a 40 per cent spergon® salve, who developed a persistent diarrhea and a pediatrician could find no reason for the diarrhea and when the use of spergon® was discontinued, the child began to improve immediately and was well in a few days.

Dr. D. Truett Gandy, Houston, Tex.—I should like to mention the purple X globe and its use. Dr. Dennie had a report lauding this instrument highly. But my experience with it has not been at all happy. It produces a quality of fluorescence far inferior to the conventional Wood's light, and it gets entirely too hot. My patients have not cared for it.

Dr. M. Allen Forbes, Jr., Austin, Tex.—I have had good luck using the purple light bulb. I keep them in my office and give them to the mother, but one must be careful of the type of individual to whom one gives it. I instruct the mother to put a wire screen around the bulb and to epilate the fluorescent hairs every five to 7 days. And I inspect the patient every two weeks at the office. I think I have been able to shorten the cure of tinea capitis by the use of the purple X bulb.

Dr. Rankin (closing).—Dr. Noojin asked about the length of time required for cure. The shortest period of time that we have on record was two weeks, which was in a case of Microsporon canis. Of patients who were affected with Microsporon canis, the average was approximately one month; but we had a failure in the Microsporon canis group.

In the Microsporon audouini group of cases, the shortest period of time for cure was one month; the average time was three months. However, some patients were treated for as long as seven months and eventually were cured. That is as nearly as I can answer the question of how long. Spergon® is not a panacea. Cooperation from the family is essential, no matter what the medication may be.

Dr. London asked about the matter of higher concentration of spergon® and its penetration. We quickly found in these experiments that a water miscible ointment base gives better penetration. Higher concentrations were used with good results.

We have observed no systemic reaction to this drug. The reports on toxicity by McGavick and others, failed to show any absorption of spergon® by way of the skin; so we must assume, from their work, that it is nontoxic.

As for its being an irritant: Dr. Gardner Hopkins, of New York, during the war, spent a great deal of time at Fort Benning studying mycologic problems. He had some experience with the use of spergon® at that time. He failed to notice any irritant quality of spergon® in ointment bases, and this has been our experience, except in a group of patients who used a 40 per cent concentration of the chemical, kerion developed.

I personally am a great believer in manual epilation. Since it is impossible to go into the home, and yet you see obvious failure to epilate on return to the clinic, there is no way to evaluate the matter of manual epilation in these patients. All patients are instructed in manual epilation, and that is one of the most important parts of the treatment of this disease.

Carbowax,® of course, has good penetration, does carry spergon® in and allows for its better activity.

We have not seen any systemic toxic reactions.

And lastly, we firmly believe that the Wood's filter (if slightly more expensive) is a more efficient means of examining a patient's head for fluorescence.

TREATMENT OF LATERAL DEVIATIONS*

By WELBORN W. SANGER, M.D.
Oklahoma City, Oklahoma

At this time and place, there is hardly any need to discuss the frequency, or importance of, lateral deviations of the eyes. Strabismus is probably not secondary to either cataracts or glaucoma in the thoughts and writings of practicing ophthalmologists.

Strabismus, more commonly known as squint, or tropia, is a manifest faulty position of the eyes which prevents the visual lines from crossing at the fixation point. Guibor's shorter definition of strabismus is;

"A symptom complex in which the two eyes do not focus an object simultaneously."

*Read in Section on Ophthalmology and Otolaryngology, Southern Medical Association, Forty-Fourth Annual Meeting, St. Louis, Missouri, November 13-16, 1950.

This paper will be concerned with convergent and divergent strabismus only, and will not discuss the phorias, vertical strabismus or cyclotropia.

It is obvious that many important points will not be touched because of the limited time for discussion.

Before the treatment of lateral deviations is considered we should think of the different types of strabismus and a little of their etiology and pathology.

There are two general classes of lateral strabismus: (1) convergent and (2) divergent. Each of these may be (1) monocular, (2) alternating, (3) intermittent, (4) constant.

Kramer has given further subdivisions.

Convergent strabismus: (1) concomitant (mechanical), (2) accommodative, (3) paretic, (4) neurogenic, (5) any combination of the above four.

Divergent strabismus: (1) concomitant (mechanical), (a) divergence excess, (b) convergence insufficiency, (c) combination of (a) and (b); (2) accommodative, (a) uncorrected myopia, (b) overcorrected hyperemia; (3) paretic; (4) concomitant-accommodative.

It is obvious that the treatment of each of these types is different.

Concomitant Strabismus.—A congenital or acquired neuro-muscular anomaly of one or more of the extra-ocular muscles is commonly called mechanical strabismus, since it may be caused by a structural, or mechanical, anomaly of the extra-ocular muscles. The same amount of deviation is measurable in the entire field of fixation. It is roughly the same, regardless of which eye is fixing, and may be monocular or alternating. It is commonly hereditary in origin. However, a functional type of squint, particularly that caused by refractive error, while at first intermittent, may become constant and assume the characteristic of a concomitant squint. The same holds true of a paralytic (non-comitant) squint in which the paresis may have recovered but the contracture of the antagonist, or yoke muscle, remains, causing anatomical changes in the muscle structure. The strabismus then has all the characteristics of a purely concomitant strabismus.

There may be a faulty insertion of muscle or muscles, abnormal length or elasticity of a muscle, a deficient tonus of the muscle, or the amount of facia and retrobulbar tissue may be abnormal.

(1) Concomitant convergent strabismus is characterized by its constancy. It is present at all times with, and without, glasses, regardless of whether the patient is tired or rested.

Treatment is both orthoptic training and surgery. Glasses may or may not be worn, as the refractive error plays no part in a purely mechanical convergent squint. But if the hyperopia, or astigmatism, is over one or one and a half diopters I always prescribe glasses, with full correction, after cycloplegic refraction with atropine.

Suppression and amblyopia are frequently present, depending on the duration of the strabismus and the age of onset.

Surgery should be performed early, preferably at the age of 2, 3 or 4, and then, ideally, post-operative orthoptics training immediately instituted to attain a functional cure.

Parents and other physicians should be educated to have children examined by an ophthalmologist as soon as there is any question regarding their eyes.

Total occlusion of the better eye should be done early, from one to four months at a time, depending on the degree of amblyopia and the age of the patient. Occlusion of the better eye for 2 or 3 hours a day, or just on week-ends, is useless and a bother to the mother and the patient. Occlusion should be done from the awaking hour until the patient gets in bed for sleep.

Occasionally, in the early concomitant squint, which has been operated upon between the ages of 2 to 4, the patient will develop a cosmetic and functional cure without orthoptic training.

The various methods of orthoptic training will not be discussed, because it is almost always, (as it should be) done by a trained orthoptic technician. We all realize that, except in the larger centers, our patients, for one reason or another, are not given the benefit of orthoptic training seriously enough, long enough, or often enough.

(2) Accommodative convergent strabismus is caused by a disturbance of the accommodation-convergence ratio in an effort to compensate for uncorrected hyperopia or anisometropia. As it does not occur in all patients with uncorrected hyperopia the efficiency of fusion may be the important factor. The squint is intermittent, being present only when the patient is accommodating.

Treatment consists of (1) correction of the refractive error, and (2) orthoptic training. Surgery is contraindicated.

Amblyopia, if present, should be treated first. Full (atropine) correction is given to be worn at all times. If the eyes are not straight while accommodating for near, a bifocal of +2.00 or +3.00 add is usually prescribed. The fusion training should be left in the hands of the orthoptist.

(3) Mechanical-accommodative convergent strabismus is a combination of the mechanical and accommodative and is very probably the most frequently seen in practice. The squint is constantly present but is variable in its amount or degree. Surgery is indicated to correct the amount that is mechanical. The amount that is functional or accommodative should be treated by orthoptic training. Full correction of the refractive error may be necessary at first but the aim is to eliminate suppression when the patient is accommodating by dissociation exercise and finally the elimination of glasses.

(4) Neurogenic convergent strabismus is an intermittent type believed to be caused by exaggerated or excessive innervations from the convergence center. It is often combined with other neurogenic factors wherein other organs receive a greater than normal innervation to the motor muscles producing an overaction of other body functions. The chief characteristic of this type is its variability. The strabismus is not always present depending on the state of tonicity in general and whether the patient is stimulated or relaxed. The patients are usually quite unstable emotionally but are also quite intelligent.

Treatment.—Good hygiene and an environment with the least amount of psychic and emotional stress and excitement are emphasized. Orthoptic training is indicated for the ocular condition. Surgery is contraindicated. Full correction of the refractive error and often bifocals for near work should be prescribed.

(5) Paretic convergent strabismus results from a paresis or paralysis of the abducens, or sixth, nerve. The location and type of lesion may affect the amount of deviation. These are most often caused by lues and trauma, and occasionally by neoplasms.

Treatment.—Relieve the causative factor if possible. Occlusion of the paretic eye is advised to prevent the annoying diplopia and to lessen the likelihood of a permanent secondary contracture of the yoke muscle. Orthoptic training is sometimes indicated when the paretic muscle has recovered. In the late stages of paresis the deviation may have the characteristics of a mechanical or comitant strabismus. Here it is surgically and orthoptically treated like any other comitant strabismus.

(2) DIVERGENT STRABISMUS

(1) *Concomitant (Mechanical) Divergent Strabismus with Divergence Excess.*—The measurements in all fields are approximately the same and the deviation outward is greater for distance than for near. Unlike comitant convergent strabismus these cases often have fusion for near because of the voluntary act of convergence.

Treatment is orthoptic and surgical. Of prime importance is the correction of abnormal retinal correspondence, and amblyopia exanopsia, if present.

(2) *Comitant (Mechanical) Divergent Strabismus with Convergence Insufficiency.*—Here the near point of convergence is remote and the deviation is greater for near than for distance.

Treatment.—If the patient is a high myope (which he usually is) the refractive error should be corrected with full correction (there is no reason to deduct a quarter of a diopter). If hyperopic, either no glasses are prescribed or at least the amount of correction is prescribed, which gives the patient comfort and efficiency. The full amount of astigmatism may be prescribed in all cases. Orthoptic treatment should be started at once.

(3) *Comitant (Mechanical) Divergent Strabismus with Divergence Excess and Convergence Insufficiency.*—This type is very common. The treatment depends on the variety of findings, a thorough history, and knowledge of the patient. These children are usually over 7 or 8 years of age. The divergence excess usually develops first. Often the strabismus becomes constant and has been allowed to exist for some time before the ophthalmologist is consulted.

The squint may be greater, less than, or the same, for near as for distance. Prism convergence is low; divergence is high; the near point of convergence is remote and the squint may be constant, monocular or alternating.

If the divergence is constant and with a high amblyopia, occlusion then surgery followed by orthoptic training should be done. If the devia-

tion is intermittent and some fusion is present, the suppression should be treated before the surgery.

(4) Accommodative, divergent strabismus may be observed in very young patients with uncorrected myopia and in older patients with overcorrected hyperopia or perhaps in patients with accommodative convergent strabismus who have had a recession of one of the medial recti.

Diagnosis can be made in the myope when the patient is accommodating maximally and wearing full correction and there is little or no deviation as revealed by the cover test. The greatest deviation is shown while under atropine and wearing no correction. The converse is true in hyperopic patients, that is while accommodating maximally without correction the cover test shows little or no deviation. Greatest deviation will be found while the patient is under atropine and wearing full hyperopic correction.

The squint is absent when myopic correction is worn or when the hyperopic correction is not worn.

Prism convergence may be deficient or normal.

Near point of convergence may be remote or normal.

Prism divergence is excessive or normal.

Treatment consists of full correction for the myope, or a reduction, or elimination of, hyperopic correction. Anti-suppression and fusion training can firmly establish fusion amplitude and stereopsis.

Surgery should not be done in the purely accommodative type. However, surgery is often indicated at school age when the condition ceases to remain purely accommodative and a concomitant factor has developed. Here the surgery should aim to correct the concomitant part only.

Mary E. Kramer in her book on "Clinical Orthoptics" says:

"Divergent strabismus with convergence insufficiency is sometimes very obstinate to treat and cure. It takes a great deal of effort on the part of the patient and much drive and perseverance on the orthopist's part to develop the convergence to normal, especially in children under seven. Many of these patients are of a phlegmatic type. Frequently patients have a fear or distaste for convergence, particularly for voluntary convergence, instilled in them by someone who pointed out to them that if they crossed their eyes they might 'lock' and remain 'crossed.' These fears and phobias must be recognized and intelligently, and diplomatically, worked out lest they be a stumbling block to a successful cure."

(5) Paretic divergent strabismus may be caused by:

(A) Third nerve paralysis.

(B) Paralysis of medial rectus (rare).

(C) Paralysis of convergence (supranuclear).

(D) Internuclear paralysis.

Treatment of ophthalmoplegia is medical and surgical, certainly not orthoptic.

Search for, and medical treatment of, the cause should be instituted.

(A) If ptosis is not marked, occlusion may be necessary because of the troublesome diplopia.

(B) In the medial rectus paralysis, occlusion is necessary because of the troublesome diplopia. Prisms should not be worn. Surgery is indicated in 6 months to a year if the condition does not cure itself.

(C) In convergence (supranuclear) paralysis (rare also) the removal of the cause should be attempted. The center for convergence is thought to be in the region of the corpora quadrigemina. Neither orthoptics, nor surgery, is of any value.

(D) *Internuclear Paralysis.*—These cases are so rare and treatment so unsatisfactory that they will not be discussed.

Non-surgical treatment of lateral strabismus can be summed up as:

(1) Evaluation of the case and improvement of environment.

(2) Refraction.

(3) Occlusion, to correct amblyopia and establish normal retinal correspondence.

(4) Orthoptics.

SURGERY OF THE LATERAL DEVIATIONS

When successful, surgery of the eye muscles is one of the most gratifying procedures in the field of medicine. When unsuccessful it is quite annoying and disappointing. As a rule, the results of experienced surgeons are good. The patients are most grateful and the surgeon has a justifiable sense of satisfaction greater than that by doing most other types of surgery.

There is always an uncertainty in operating for strabismus. This should be explained to the patients or parents. They are told that muscle surgery is not an exact science, as in banking, where if $10.00 is deposited and $15.00 later we have exactly $25.00 in the bank. Not so with muscle surgery. They are further informed that we have

certain principles to follow, but if exactly the same surgical procedure is done on three different patients with approximately the same deviation, one may be overcorrected, another undercorrected and the third may get a perfect surgical result.

I believe White's principle of expecting 4 to 5 prism diopters correction for each millimeter of recession and 3 to 4 prism diopters for each millimeter of resection is a good guide, but, of course, it is not always accurate.

Scobee agreed with Chavasse (1939) in saying:

"The aim of operative treatment is immediately to supplement other reputable treatment, almost exclusively optical, which has failed to straighten the eyes which are, or have been made by occlusion, as nearly equal in vision and free from perverted reflexes, that is, abnormal retinal correspondence, as circumstances permit. If the patient is young enough, it may allow the constant play of normal stimuli to elicit and even develop the normal binocular reflexes. Operative treatment may merely suffice to place correction of the deviation within the capacity of full optical treatment. Or it may in some cases make optical treatment no longer necessary."

The uncertain tenotomy of the medial rectus has been abandoned by most surgeons, perhaps by all. The recession procedure is an excellent replacement for the tenotomy. The internal rectus is usually recessed not less than three, nor more than five millimeters. The antagonist usually has to be resected, advanced, tucked or cinched. My favorite of these is the resection, occasionally combined with an advancement.

My only experience with the cinch operation was in an army hospital when I assisted a young ophthalmologist who was a patient in the hospital with nephrolithiasis. He claimed only very limited experience with the cinch procedure. The result was not encouraging enough for me to use it again.

It is obvious that no one operation will cure all types of strabismus. It is inadvisable to operate with less than three examinations of the patient. First, the deviation is measured by the cover test, in the six cardinal directions without a cycloplegic, with and without glasses. The measurements are repeated under cycloplegic, and at the third examination a fairly accurate evaluation of the case should be had. Careful and repeated studies should be made of the near point of convergence. This is perhaps the most important consideration regarding upon which lateral muscle to operate. The near point of convergence may be poor in a convergent squint, in which case the medial recti should not be recessed to weaken further a weak convergence. In a convergent squint where the deviation is greater for near than for distance, we term it a convergence excess. Many surgeons recommend bilateral internal rectus recession. I seldom do this procedure. Instead I usually recess the internal rectus and resect the external rectus on the poorer eye because of the danger of too great weakness of the convergent function.

In a few cases of a very high degree of external strabismus with amblyopia of long standing, I have done a complete tenotomy of the lateral rectus with good cosmetic results. In the high lateral deviations, a vertical deviation may be overlooked and after the lateral correction the vertical component becomes apparent.

As Post has pointed out the one general rule is to correct the greater defect first. The surgery of the horizontal muscles is usually done first. Many who do not carefully analyze their cases but operate only upon the horizontal deviations get a good cosmetic result, but not a physiologic cure. Post further says:

"It is important to remember that correction of the lateral deviation in cases in which there is also a vertical deviation may either increase or decrease the latter, depending on the muscles involved. For example, if a vertical rectus is involved, the deviation will be greater after correction of esotropia, because returning the eyes to the primary position will bring them nearer the field of maximum action of the vertical recti; whereas, if the difficulty is with an oblique, the effect of the correction of esotropic abnormality will be an apparent lessening of the strabismus caused by the abnormalities of an oblique muscle."

Where the esotropia is greater for distance than for near, it is considered good surgery to do a bilateral resection of the lateral recti, but the results are usually a considerable under correction unless the antagonist is weakened. So again, I usually operate upon the medial and lateral recti muscle of one eye rather than do a bilateral resection or a bilateral recession.

If the exotropic patient is a fairly high myope and the esotropic patient a moderately high hyperope the surgeon has greater leeway. For example, if the esotropia is overcorrected, a reduction in the strength of lenses, or leaving them off entirely, will be of value in combating the overcorrection. The reverse is true in undercorrection. The same holds true in over and undercorrection exotropia. Give full correction in undercorrected myopia and leave off the glasses in

overcorrected exotropia. Atropine is also a useful drug in undercorrected esotropia cases.

Perhaps the most difficult surgical cases are the ones of small degree with no refractive error. I recently recessed the medial rectus 3 mm. on the previously amblyopic eye of a six-year-old boy with 15 to 20 prism diopters esotropia. In one month the final result was 15 to 20 prism diopters esotropia. In this case I was especially careful to insert my sutures in the tendon very near the insertion and to cut the tendon close to its attachment. All check ligaments and muscle slips were severed. I have no explanation of why there was no improvement in the deviation. I can conceive that a muscle may slip backward from where it is sutured but cannot stretch my imagination enough to believe that a muscle could slip forward to its original insertion.

The method of Post and Scobee of waiting until the patient is under general anesthesia to determine just what surgical procedure to use is seldom, if ever, mine. They note: (1) the difference in deviation; (2) the action of the eye when pressure is made in the canthus opposite the deviation; (3) the condition as regards the check ligaments; and (4) the elasticity of the severed muscles.

Scobee says that no successful surgeon can ever decide exactly how many millimeters of surgery he will do in every case prior to operation, and that Kirby and White agree with him. I believe they cannot decide exactly the amount in every case, but after repeated cover test examinations they should decide the procedure and nearly the amount.

Scobee says that he operates upon all strabismus cases, both adults and children, under general anesthesia. If they do not want a general anesthesia they are told to get another doctor. I prefer local anesthetic of 0.5 per cent pontocaine® and retrobulbar injection of 2 per cent procaine hydrochloride in adults and most children over 15. The youngest local case was a stoical, red-haired girl of thirteen. With preoperative sedation of pentobarbital sodium and 50-100 mg. demerol®, the operation is almost painless.

All writers agree that the technic of the operation is of far less importance than the diagnosis that dictates which muscles, what procedure, and how much should be done. The main points are to place the muscles on the same horizontal level; to be careful not to put the sutures too far back from the insertion in a recession; and then to secure the muscle firmly in resection or advancement.

There are almost as many ways of putting in sutures as there are ophthalmic surgeons. I have used many different technics and have tried to develop a routine technic and stick with it, but at the present time have not done so.

The episclera and scleral fibers are very strong and a deep bite with the needle is unnecessary to secure firm fixation. It should be understood that the needle and suture should be visible through the sclera at all times. On two occasions my needle has slipped through the sclera, penetrating into the eyeball, with no perceptible ill effects.

In doing recessions it is important to cut all abnormal muscle slips between the muscle and the eyeball and all check ligaments to enable the muscle to retract freely into the orbit.

In what appears to be a paralysis of the external rectus, where the eyeball cannot be moved laterally past the midline, I concur with Payne and with Post that it is best to do a recession of the internal and resect the external rectus which often make a Hummelsheim (transplanting of the lateral halves of the superior and inferior recti) operation unnecessary.

O'Connor says that he does the Marlow occlusion test to prove his operative results, figuring that his work is not finished until the patient tests within the allowable variation from normal behind the patch. He further explains,

> "This shows two things: (1) There is no need to fear the production of the opposite condition, provided of course, that the right operation has been done at the right place. (2) The test behind the patch is the true one, exactly as the refraction under cycloplegic is the true test in that respect."

I know of no surgeon who uses this method as a final test for a cure. The results of over, or under, correction are obvious, and in the case where the cover and Maddox rod tests show only a few prism diopters deviation I am content to accept these figures as being accurate.

In a series of 176 cases of lateral deviation, operated upon in the army, seven cases were overcorrected. This proportion of overcorrection is far too great to report without embarrassment. The fact that the men were sent out and in on short notice and that there was too little time for proper preoperative work-ups is a poor excuse.

An undercorrection is much more to be preferred than overcorrection. The surgeon should be content with an undercorrection that may be amenable to further an operation rather than try to accomplish too much and find it difficult to reconstruct.

Several of the overcorrected cases were re-operated upon one to three times, often with little effect. Kirby has given us the reason why little is accomplished in the attempt to undo an over-correction. He gives us "The principle of Tenon's capsule transplant for the relief of muscular adhesions hindering muscular action." The ability to bring a muscle anteriorly to a previously placed normal or abnormal insertion in the sclera was exemplified by Berens.

"If the denuded area on the sclera from which is removed the abnormally retroplaced or adherent muscle is not covered by Tenon's capsule, the attempt to move the muscle forward to a new or more anterior position will fail, for an adhesion will form between the belly of the muscle and the denuded area where they came in contact. The insertion will remain where it was and the muscular action and function will not be improved sufficiently to be satisfactory. The technic of covering the denuded area of sclera with a free, pedunculated, or sliding graft of Tenon's capsule, utilizing tissue to which the muscle is normally accustomed as a sheath, and to which it will not adhere, is well described by Berens."

In the past five years this technic has been used in a few cases with very satisfactory results.

CONCLUSIONS

(1) Lateral strabismus cases are among the most frequently encountered, and most interesting types of cases in ophthalmological practice.

(2) The treatment of a purely mechanical strabismus is by surgery and orthoptics. Refraction plays no part in the cause of treatment.

(3) Full cycloplegic correction should be given to a myope with lateral deviation and to a hyperope with medial deviation.

(4) Surgery is contraindicated in purely accommodative tropias.

(5) Treatment of ophthalmoplegias is medical and surgical, not orthoptic.

(6) Tentomy of the medial rectus has been replaced by the recession operation.

(7) Combinations of accommodative and mechanical strabismus are the most frequently encountered.

(8) The near point of convergence is a most important factor in every squint.

(9) The greater defect, either vertical or lateral, should be corrected first.

(10) Correction of a lateral defect will either increase or decrease a vertical deviation depending upon the muscles involved.

(11) The most difficult surgical cases are the ones of small degree with no refractive error.

(12) The technic of operation is far less important than the diagnosis.

(13) To get maximum effect from a recession it is necessary to cut all abnormal muscle slips and all check ligaments.

(14) An undercorrection is much preferred to overcorrection.

(15) A graft of Tenon's capsule is a valuable aid in preventing adhesions between the muscle and sclera in re-operating upon overcorrections.

(16) Parents and physicians should be instructed to refer the case to a competent ophthalmologist as soon as any ocular deviation is noticed.

(17) Results of strabismus surgery are seldom perfect, but as a rule, the results are quite satisfactory. The patients are usually very grateful.

PERIARTERITIS NODOSA TREATED WITH ACTH*

REPORT OF CASE

By BENJAMIN F. MARTIN, M.D.
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Periarteritis nodosa is a widespread necrotising polyarteritis affecting chiefly the small and medium sized vessels. There is no uniform clinical picture, for the disease may affect the vessels of one or several organs or systems in the body causing a complex clinical picture. It is said to be more common in males in the fourth and fifth decades. The etiology has not been established. Infections, intoxications and viruses have been suggested as causative factors.[1 2 3] Rich[5] and others have produced evidence that allergy plays an important role in its pathogenesis.

Because of the protean characteristics of the disease and its ability to simulate many other

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clinical entities, the diagnosis of periarteritis nodosa is made frequently at the postmortem examination, and this, together with improved diagnostic facilities, probably accounts for the apparent recent increase in the incidence of the disease.

Because the necrotising process may affect the arteries anywhere in the body, there is no uniform clinical picture; however one particular organ or system is often more affected than the rest. Arkin[4] listed the organs attacked most frequently: the kidney 80 per cent; heart 70 per cent; liver 56 per cent; gastro-intestinal tract 50 per cent; pancreas 25 per cent; mesentery artery 30 per cent; muscles 30 per cent; peripheral nerves 20 per cent; and central nervous system 8 per cent.

The more frequently encountered clinical findings are: temperature elevation; increasing generalized weakness with weight loss and later muscle wasting; leukocytosis with eosinophilia; elevated sedimentation rate; albuminuria, hematuria, anemia; hypertension, epigastric pain, tachycardia, polyneuritis, polymyositis; headache, and subcutaneous nodules. The only definite laboratory aid is biopsy of cutaneous lesions or of skeletal muscle.

Periarteritis nodosa has recently been grouped by some observers under the classification of "collagen diseases," and adrenocorticotrophic hormone has been reported to be effective in this group. Since no effective therapy is known, it was decided to use that drug in the following case:

A fifty-two-year-old white woman, a registered nurse, was admitted to the hospital on August 28, 1950, with a history of pain and soreness in the left foot, ankle, and thigh, and across the shoulder girdle of approximately 4 weeks' duration. The pain was not persistent, was relieved temporarily by aspirin and she had continued her work until one week prior to admission, when she went to bed at home. At this time she developed generalized malaise with increasing pain and tenderness in the extensor muscles of the left thigh, over the biceps in both arms and across the shoulder girdle, an irregular temperature elevation to 102° and night sweats.

Physical examination revealed a well developed and well nourished, alert and cooperative white woman. The temperature was 100 degrees; the pulse 80 and the respirations 20. The skin was moist and warm. The pupils were equal, regular and reacted to light and accommodation. There was moderate narrowing of the retinal arterioles. Median moist rales were heard at both bases, but there were no abnormal percussion notes. The heart was not enlarged to percussion, the sounds were distant and there was a grade II systolic murmur at the apex. The blood pressure was 130/70. The liver and spleen were not palpable, the abdomen was entirely negative and rectal and vaginal examinations were normal. The most striking feature was the marked pain and tenderness found on palpating the extensor muscles of the left thigh, the right and left biceps and the muscles making up the shoulder girdle.

The red blood count was 4,300,000, hemoglobin 78 per cent or 12 grams; white blood count 13,400 with segmented forms 70 per cent; stabs 5 per cent; lymphocytes 21 per cent and eosinophils 4 per cent. The urine was not abnormal; sedimentation rate was 22 mm. per hour; nonprotein nitrogen 30 mg. per cent; blood Kahn negative; agglutination for undulant fever and other infections were negative; serial blood cultures were negative. The electrocardiogram was within normal limits.

She received 1,600,000 units of penicillin and 3 grams of chloromycetin daily for one week. During this time her temperature varied from normal to 101° daily. The pain and tenderness over the left leg and arms became exquisite and the patient assumed a flexed and pitiful position in bed, crying out even with movement of the bed covers. At this time there was noticeable wasting of the muscles involved. Her red blood count varied between 2.9 and 3.3 million. The white blood count was between 11,000 and 16,600; with an eosinophilia of 12 per cent on one occasion. The sedimentation rate rose to 54 mm. per hour, and the urine showed a trace of albumen and numerous white blood cells.

She was given 250 cc. of whole blood by transfusion on two successive days and on the thirteenth day, adrenocorticotrophic hormone was begun, using ten mg. every six hours. The response was striking; the temperature returned to normal within the first twenty-four hours; the general appearance of the patient was markedly improved; she was able to sit in bed alone and to move her arms and legs with little discomfort. On the second day of treatment with ACTH the patient said: "I feel so good I am almost hysterical"; she was able to get out of bed, walk around the room and write several letters. At this time there was only mild tenderness over the affected parts, and her chief complaint was weakness in the arms and legs. On the third day of treatment the red blood count was 3.8 million; hemoglobin 10.5 grams; white blood count 13,000; segmented forms 60 per cent; stabs 5 per cent; juveniles 1 per cent; lymphocytes 31 per cent; and eosinophils 3 per cent. The sedimentation rate was 52 mm. per hour. This remission continued for six days after which she developed a chill, temperature elevation to 101,° and an acute exacerabation of severe pain in the arms and legs. The temperature rose to 103° on the following day.

The ACTH was increased to 15 mg. every 6 hours and, as on the previous occasion, there was an abrupt return of the temperature to normal with the same remission of symptoms as described before. There was increasing atrophy of the deltoid and biceps muscles bilaterally. This remission continued for four days when again on the twelfth and thirteenth days of treatment she had a chill and temperature elevation to 102° and a recurrence

of marked pain and tenderness of the upper and lower extremities, marked weakness of the extensors of the left forearm and wrist, and a patchy impairment of sensation.

Muscle biopsy from the right biceps muscle showed the following:* The muscle fibers show recent degeneration; no evidence of collagenous changes. There are scattered small foci of acute inflammation surrounding the smallest arterioles; no large arterioles are present in the sections. The infiltrating cells are chiefly polymorphonuclear, with few macrophages and lymphocytes. No eosinophils nor trichinella are seen. These findings are compatible with periarteritis nodosa or with acute disseminated myositis. No specific diagnostic features are present.

The ACTH was increased to 20 mg. every 6 hours and a remission of temperature and clinical findings for 3 days followed this; then for the third time, on the sixteenth day of ACTH treatment, she had a chill and temperature elevation with recurrence of pain and tenderness which now had become generalized and exquisite. Her course continued downward during the next seven days; the hormone failed to bring about even temporary remissions and large doses of opiates failed adequately to control her pain. On the thirty-fifth hospital day she developed an intense headache which was almost immediately followed by vomiting and deep unconsciousness. Her blood pressure rose to 265/160 and she died 36 hours later without regaining consciousness.

At postmortem the patient was found to have a massive subarachnoid hemorrhage which was secondary to a generalized vascular disease having the classical features of acute periarteritis nodosa. This hemorrhage accounted for the terminal manifestations.

COMMENT

A case of periarteritis nodosa in which the chief clinical manifestations were due to involvement of the neuromuscular system is described. With the administration of adrenocorticotrophic hormone, striking and prompt clinical remission was observed, with definite improvement of peripheral neuropathy; however this remission was not permanent. Should curative results be obtained with ACTH it would seem that therapy should be intensive and should be used early in the course of the disease.

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*Examination made by Virgil H. Moon, M.D.

ANALYSIS OF CLINICAL DATA ON 500 CHILDLESS COUPLES: FERTILITY RESULTS*

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For the last 15 years our group has been interested in the study of the infertile couple. In 1941,[1] one of us (E. C. H.) presented before this Association an analysis of some data of the first 100 completely studied couples. Several other general contributions, including "Facts for Childless Couples,"[2] subsequently have been made. Five hundred couples now have had complete sterility investigations. We plan a series of reports on the accumulated data of these 500 couples. This presentation will be limited to a comparison of results (pregnancy or no pregnancy) with various general considerations as time-age relationships, previous urologic and gynecologic operations, urologic, organic and gynecologic diagnoses, confirmed or established at the time of the original survey, and the estimated prognosis given the couple at the termination of the sterility investigation.

SCOPE OF SURVEY

Before this Association in 1944,[3] one of us (E. C. H.) discussed "Minimal Standards for Sterility Surveys." Our diagnostic efforts through the years have been essentially similar to those presented in detail at that time. We will recapitulate briefly. Prior to the onset of our investigation, we make it clear to the couple that the adequate study of sterility is a bilateral affair. We try to study simultaneously the husband and the wife. Investigations of the husband include complete history, general physical examination, routine laboratory work, basal metabolic determination and seminal evaluation of one and preferably more specimens collected by masturbation or withdrawal. More recently serum cholesterol levels have been determined routinely. Roent-

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genogram of the sella turcica is obtained when it is thought indicated. The wife receives the same general workup, save her special studies include postcoitus test, tubal patency determination, and endometrial biopsy. More recently, basal body temperature determinations have been used. As a rule, tubal patency is evaluated by hysterosalpingography under fluoroscopic control. Carbon dioxide insufflation usually is reserved for therapy. When the survey is complete, the couple is seen together with the physicians who were responsible for its survey. The facts are reviewed, treatment outlined and an attempt at estimation of prognosis is made.

ANALYSIS OF PREGNANCY RESULTS

The 500 infertile couples of this study constitute a totally unselected group. All couples on whom the survey studies were completed are included. No unilateral surveys are counted, and couples in whom the prognosis was known to be poor prior to the initiation of study are not excluded. Absence, complexity, length of treatment, or shortness of follow-up after the end of the survey did not afford an excuse for elimination from this study. The only reason that a couple which initiated the survey was not considered was noncompletion of the survey. We have found that very few public clinic couples have sufficient interest or understanding to carry the survey to completion. We have made every attempt to get complete data rather than assume an early pessimistic outlook on the basis of initial nonpatency of the tubes or low seminal count.

Of the 500 infertile couples, 403 couples had a history of no previous pregnancy. There were, accordingly, 97 couples with secondary infertility. We know that 171 wives became pregnant either during or following the infertility survey, an incidence of 34.2* per cent. Recent reports[4,5] show a 28.2 and 26.1 per cent pregnancy result in 118 and 134 couples respectively. Our follow-up of the 500 couples is incomplete and this figure does not represent the actual results. *Fig. 1* indicates the distribution of pregnancy to nonpregnancy of the 500 couples.

The outcome in 171 pregnancies is shown in *Fig. 2*. There were 126 live births and 41 patients with pregnancy wastage. Five patients are undelivered at present. This totals 172 conceptuses in 171 pregnancies as there was one set of twins. Patients were returned to their referring physicians for prenatal care.

The distribution of pregnancy wastage is illustrated in *Fig. 3*. There were 34 abortions, early and late, two stillbirths, three ectopic gestations, and two therapeutic abortions. The therapeutic abortions were done elsewhere. Again, the percentage of ectopic gestation in sterility wives is higher than in the general population of pregnant women.

TIME-AGE RELATIONSHIPS: PER CENT PREGNANCY

There are four fundamental time and age relationships which are of importance in any general

*This figure (34.2) will be called survey pregnancy per cent.

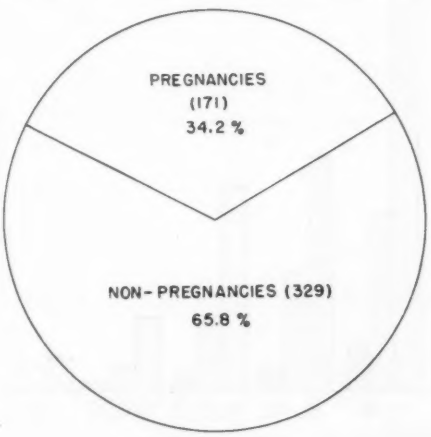

Fig. 1
Incidence of pregnancy in 500 infertile couples.

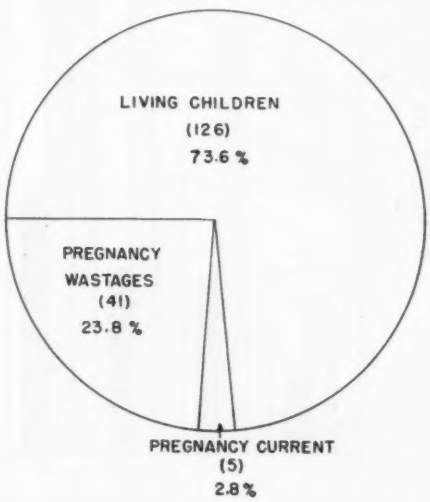

Fig. 2
Analysis of pregnancy results.

Fig. 3
Analysis of pregnancy wastage.

consideration of infertility. These are the duration of presumed sterility, the age of the wife, the age of the husband, and possibly the duration of the marriage. We will give the data of our arbitrarily selected groups of time and age, and the correlations with the survey pregnancy per cent.

The duration of marriage and presumed sterility in comparison with the incidence of pregnancy of our 500 infertile couples is shown in *Fig. 4*. The frequency of presumed sterility rises steadily from 6.2 per cent for those with less than one year of infertile mating to 27.6 per cent for three to four years. The trend then sharply reverses itself. Only five of our couples had presumed sterility of 14 to 16 years; none had more.

In general, the duration of marriage is more than the duration of presumed sterility. The duration of marriage curve roughly parallels the presumed sterility curve for the first four years.

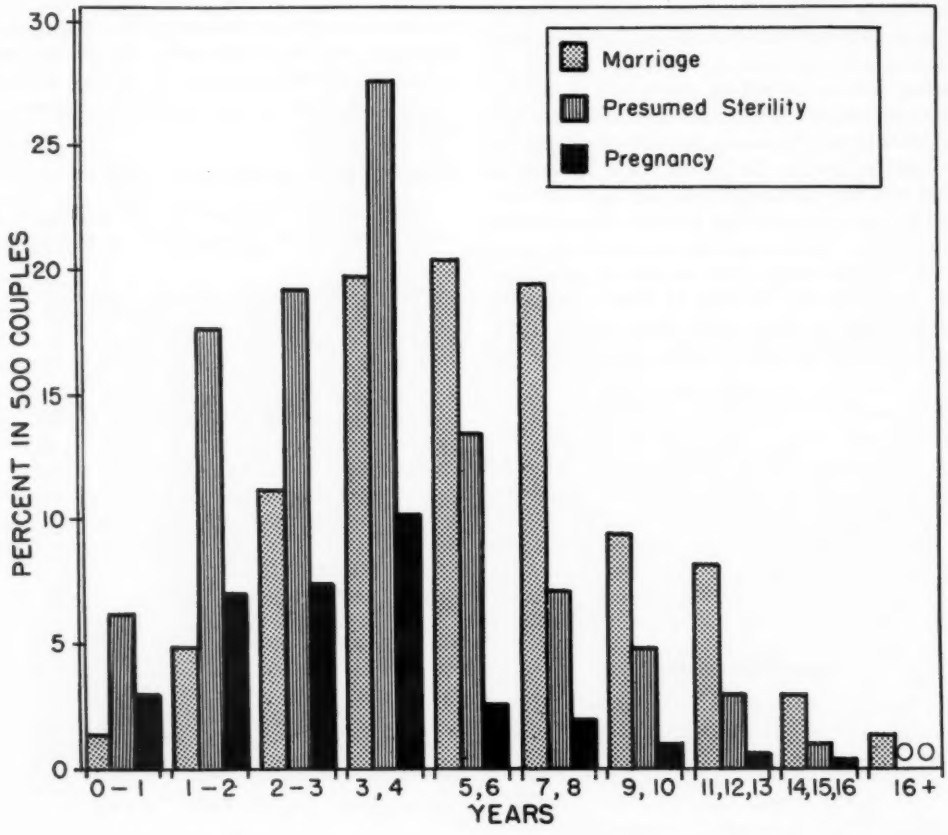

Fig. 4
Correlation of duration of marriage and presumed sterility with pregnancy in 500 infertile couples.

The incidence of marriage durations of five to six and seven to eight years, however, remains high, and does not significantly fall until nine to ten years. Of our 500 couples, 1.4 per cent had been married 16 years or more.

The fact that we have 119 couples who had a presumed sterility of less than two years should receive comment. A significant number was service couples and one could hardly invoke an assumed 2-year rule on them. Over 40 per cent of both husbands and wives had previous special sterility studies. In many of these, conditions were discovered which made further procrastination inadvisable. Furthermore, recent studies have made it reasonable to initiate infertility investigations after one year of sterile mating. Diddle, Jack and Pearse,[6] studying service wives, found that 86 per cent of multipara and 64.9 per cent of primipara became pregnant within one year when using no prevenception. Teelze, Guttmacher and Rubin,[7] from their private practice, reported that 90 per cent of women conceived within the first year without prevenception, but that it required somewhat longer for primipara than for multipara.

The pregnancy per cent in reference to the 500 couples does not give a true picture. Only 3 per cent of our pregnancies occurred in the less than one year in presumed sterility group, and 10.2 per cent in the three- to four-year group. When one considers the number of patients in each group, one sees a rather constant gradient from less than one year, when almost 50 per cent became pregnant, until 11 to 13 years when only 20 per cent became pregnant. The groups beyond that are too small to compare.

This declining pregnancy incidence is emphasized in *Table 1*. Here we have compared years of presumed sterility, number of couples in each group, per cent pregnancy in each group and the deviation of this per cent from the survey pregnancy per cent. This shows what one might expect. With a presumed sterility duration of less than one year, the pregnancy incidence is 14.2 above the survey average. This falls to a plus 4.4 for the one- to two-year group, and stays about plus 2.5 for the two- to four-year span. It then sharply declines and stays within the minus 13 to minus 14 range except for the seven- to eight-

CORRELATION OF PREGNANCIES WITH RELATION TO YEARS OF PRESUMED STERILITY

Years Presumed Sterility	Number of Couples	Per Cent Pregnancy	Deviation from Average of Pregnancies (34.2 Per Cent)
Less than 1	31	48.4	+14.2
1-2	88	38.6	+ 4.4
2-3	96	36.5	+ 2.3
3-4	138	36.9	+ 2.7
5-6	67	19.4	—14.8
7-8	36	27.7	— 6.5
9-10	24	20.8	—13.4
11-13	15	20.0	—14.2

Table 1

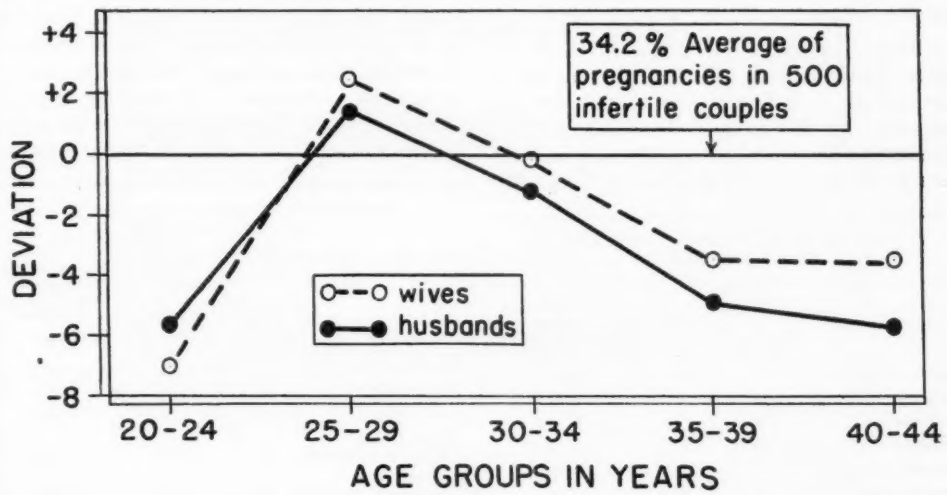

Fig. 5
Ages of husbands and wives, deviation from average pregnancy per cent.

year group. We have no explanation for this apparent alteration in trend.

For the survey as a whole, the age of the husbands is greater than that of the wives. There are 404 wives and only 298 husbands below 35 years of age. The reason that pregnancy results (*Fig. 5*) are low in the 20- to 24-year group is probably that many had histories of infection which caused their fertility status to be questioned early. After the 30- to 34-year age group there is a significant drop in pregnancy results. It may be surprising to many that males have greater deviation from the survey average than females. There were 12 males over the age of 44 and seven pregnancies occurred. The groups are so small that we did not compare them with much larger groups. This is not what might be expected and we can offer no explanation. Further analysis of our data may offer some clue.

GENITAL HISTORY AND STATUS OF HUSBANDS: PREGNANCY RESULTS

There were 43 urologic operations (excluding the urinary tract) in 39 males prior to the survey (*Table 2*). A total of 124 husbands had abnormal genital findings exclusive of testicular pathology. Comparable figures in the wives are enlightening.

Varicocele and hydrocele usually are not considered important in male infertility. Our data do not bear this out, for even varicocele, which was often unilateral, is associated with a minus 13.7 deviation. Eight hydroceles were detected and the deviation is minus 9.2.

Chronic prostatitis was diagnosed in 37 patients. Most of these were confirmed by one of our urologists. Following survey the per cent pregnancy for this group is 18.9 (minus 15.3). At examination unilateral epididymitis was discovered 24 times and bilateral seven times. The pregnancy average is minus 4.2 and minus 19.9 respectively, below survey average.

Husbands who had previous urologic operations had a minus 13.3 deviation from the survey pregnancy per cent. The number of patients with specific urologic operative procedures is small. No patients[6] who had operations for cryptorchidism succeeded in fathering a child. Fertility apparently was impaired in association with varicocele operation, for only two out of seven who had such operations are credited with pregnancies. No husbands[4] who had a hydrocele operation were successful. Pregnancy resulted in only three of 16 couples whose husbands had herniorrhaphies. We know of no explanation.

During the original examination unilateral cryptorchidism was found 10 times and bilateral once (*Table 3*). Only two of the former fathered children; neither pregnancy is attributable to therapy in the husband.

Mumps orchitis during or following adolescence occurred in 75 husbands. For this entire group the deviation from the survey average is minus 14.2. Those with unilateral disease followed by atrophy have an almost average incidence of pregnancy. Those with bilateral disease but no apparent atrophy are less fortunate, as there is only a 19.5 per cent salvage. The seminal data will be analyzed later. It seems possible that considerable testicular damage is done by mumps orchitis without atrophy.

A history of gonorrhea was obtained in 76 husbands. We attempted to distinguish between adequate and inadequate therapy. Our criteria (persistent discharge, prolonged treatment and history of apparent subsequent complications) for this are questionable. The deviation from the survey pregnancy average is minus 4.4 with those ad-

CORRELATION OF UROLOGIC STATUS WITH PREGNANCY RESULTS

	Number of Patients	Per Cent Wives Pregnant	Deviation from Average of Pregnancies (34.2 Per Cent)
Chronic prostatitis	37	18.9	—15.3
Varicocele	53	20.5	—13.7
Hydrocele	8	25.0	— 9.2
Unilateral epididymitis	24	29.1	— 4.2
Bilateral epididymitis	7	14.3	—19.9
Previous urologic surgery	39	20.9	—13.3

Table 2

CORRELATION OF UROLOGIC STATUS WITH PREGNANCY RESULTS

	Number of Patients	Per Cent Wives Pregnant	Deviation from Average of Pregnancies (34.2 Per Cent)
Unilateral cryptorchidism	10	20.0	—14.2
Bilateral cryptorchidism	1	0	—*
Mumps orchitis with and without complications	75	20.0	—14.2
Gonorrhea with adequate treatment	47	29.8	— 4.4
Gonorrhea with inadequate treatment	29	27.5	— 6.7

Table 3

judged adequate therapy, and only minus 6.7 for those with assumed inadequate therapy. This arbitrary division is not justified.

From our data a history of mumps orchitis during adolescence or later, previous urologic surgery, unilateral cryptorchidism, varicocele, bilateral epididymitis or chronic prostatitis have approximately the same impact on infertility. Gonorrhea by history, with or without apparently adequate treatment, and unilateral epididymitis have a similar but much less depressing effect.

ORGANIC DIAGNOSES: PER CENT PREGNANCY

The general health of the patient is a major consideration in the infertile couple. Diabetes mellitus occurred in only one husband; hyperthyroidism, in one wife and one husband; pulmonary tuberculosis, once in each; and hypertensive disease, in 3 wives and 30 husbands.

Obesity, underweight, hypothyroidism and hypometabolism occurred often enough to warrant evaluation (*Fig. 6*). Obesity and underweight are associated with a slight decrease in paternity percentage. Obesity apparently has a marked decreasing effect on wives, minus 10.6. Underweight wives surprisingly showed a plus 7.8 pregnancy deviation. We anticipated that both conditions would be a depressing factor. Most of these underweight patients were, in general, healthy and took an average, adequate diet. One wonders about the practicality of amplified diets, supplementary vitamins, and so forth.

The diagnosis of hypothyroidism was made on the basis of objective signs and critical evaluation of symptoms. A diagnosis of hypometabolism was made when the basal metabolic rate was below minus 15 per cent and no true clinical picture of actual hypothyroidism existed. In the male, neither hypothyroidism nor hypometabolism significantly decreases fertility. Wives with hypothyroidism or hypometabolism have an increased pregnancy rate following survey. Therapy statistics have not been correlated.

GYNECOLOGIC HISTORY AND STATUS OF WIVES: PREGNANCY RESULTS

An analysis of the previous gynecologic operations in 500 wives is informative. Two hundred and five wives (205) had a total of 288 gynecologic operations (not including simple appendectomies) prior to their sterility surveys. (Only 39 husbands had previous genital surgery.) In addition, 25 wives gave a history of serious pelvic infection as follows: induced abortion complicated by infection, 13; ruptured appendix, with resulting peritonitis, eight; and pelvic peritonitis due to other causes, four.

Operative procedures and number of patients are shown in *Fig. 7*. The pregnancy average of

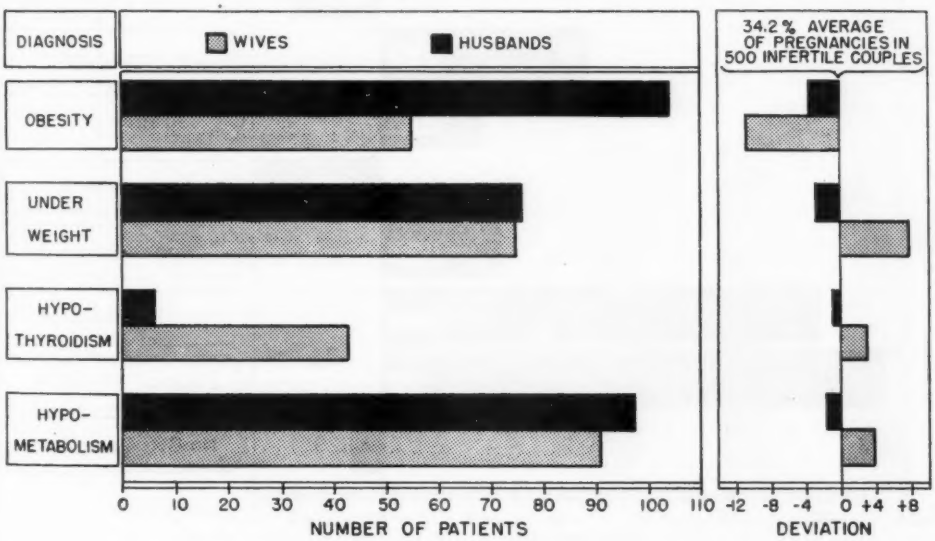

Fig. 6
Organic diagnoses during survey, deviation from average pregnancy per cent.

each group is compared by its deviation from the survey pregnancy average, 34.2 per cent.

Two hundred and ninety-five wives without previous gynecologic operations have a pregnancy incidence of 35.2 per cent.

Dilatation and curettage had been done in 115 wives, 38.3 per cent became pregnant during or following the survey, an incidence of 4.1 above the survey average. One would not expect such a procedure to affect pregnancy unfavorably. Many of these curettements had been done for cervical stenosis or as diagnostic efforts in lieu of endometrial biopsy.

Previous cervical operations were done elsewhere on 49 wives, and of these 24.6 per cent subsequently became pregnant. Suspension of the uterus had been done elsewhere in 34 wives who have a survey pregnancy incidence of 29.6 per cent. Myomectomy had been performed on five wives, two of whom later became pregnant. Various degrees of ovarian operative procedures were done elsewhere in 52 women. These had a survey pregnancy incidence of 28.9 per cent. Salpingectomy, reputedly unilateral, had been performed on 22 patients. Only 13.6 per cent of these became pregnant. One of eleven patients previously operated upon for ectopic pregnancy had a postsurvey baby. There were two wives with previous cesarean sections; both became pregnant following the survey.

A total of 392 gynecologic diagnoses were made on 295 wives at the initial pelvic examination. Diseases of the vagina or vulva are not included. There is a pregnancy incidence of 30.1 per cent. Forty per cent of the 205 wives without gynecologic diagnoses became pregnant.

The number of wives with each gynecologic diagnosis and the corresponding deviation from the survey pregnancy per cent are illustrated in *Fig. 8*.

Chronic adnexal disease markedly decreases the incidence of pregnancy. Twenty-eight wives with a diagnosis of bilateral chronic adnexal disease have a pregnancy incidence of 3.6 per cent. The 19 wives with unilateral chronic adnexal disease have a 21 per cent incidence of pregnancy.

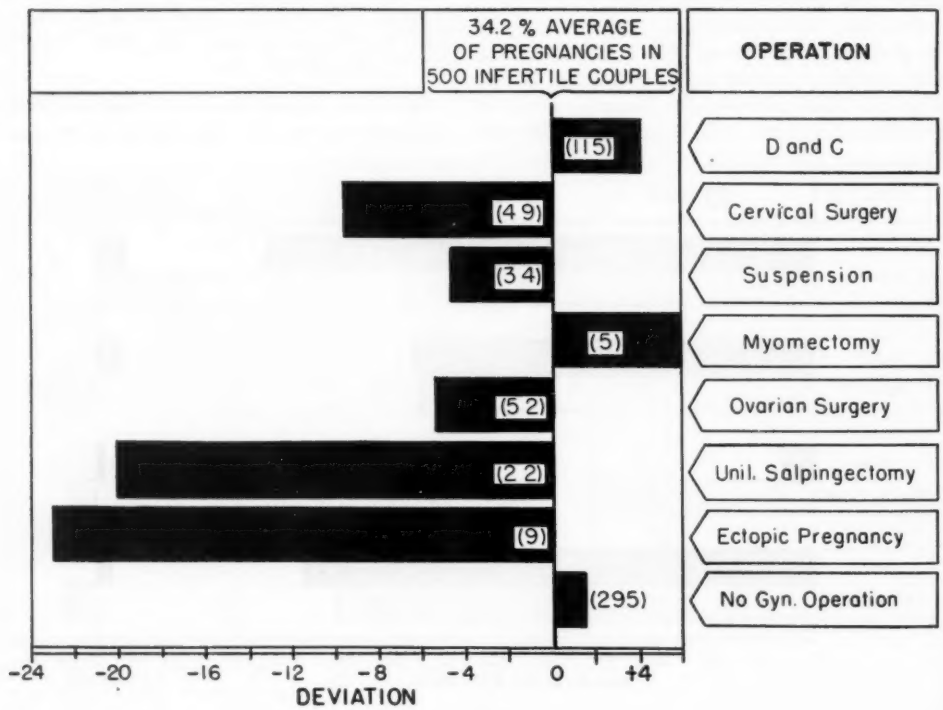

Fig. 7
Previous gynecologic operations, deviation from average pregnancy per cent.

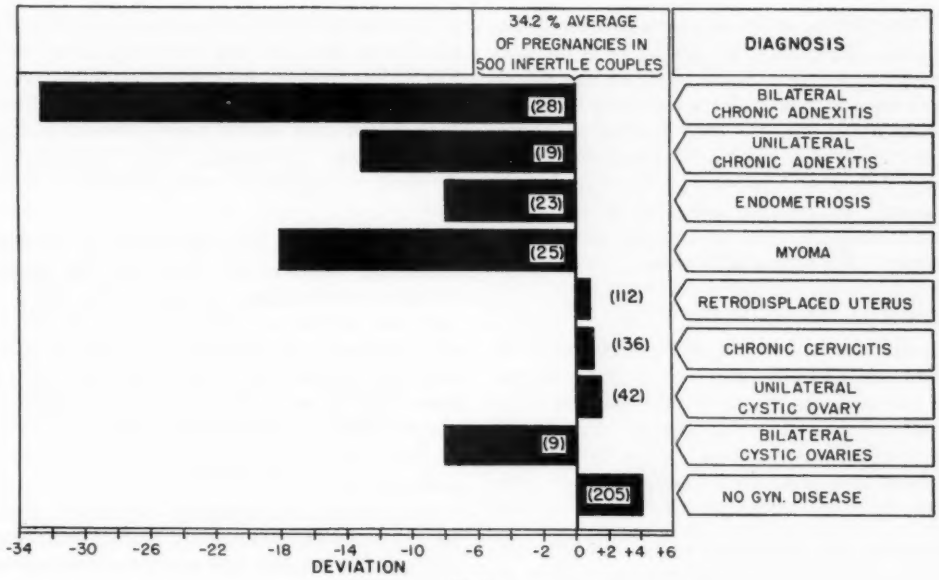

Fig. 8

Gynecologic diagnoses during survey, deviation from average pregnancy per cent.

Twenty-three wives with a diagnosis of endometriosis have a 26.1 per cent pregnancy incidence. Twenty-five wives had fibromyomata uteri at pelvic examination. Sixteen per cent of these conceived after survey. Retrodisplacements of the uterus were found in 122 wives, and 35 per cent of these women became pregnant. Varying degrees of chronic cervicitis occurred in 136 wives, who have a pregnancy incidence of 35.5 per cent. Unilateral cystic ovaries were noted in 42 wives, 35.7 per cent of whom later had pregnancies. In 9 women with bilateral cystic ovaries there was a pregnancy incidence of 28 per cent.

Wives with retrodisplacements of the uterus, chronic cervicitis and unilateral cystic ovaries have a higher incidence of pregnancy than the group as a whole though somewhat lower than those wives without any gynecologic disease.

PROGNOSIS AT FINAL CONFERENCE: PREGNANCY RESULTS

We have a final conference with the couple when the infertility studies have been completed. At this time the survey findings are reviewed, the necessary treatment is outlined and the couple is given a rough estimate of the prognosis for pregnancy. We grade (good, poor, fair) both wife and husband separately as regards his or her fertility. The future outlook for the couple is a reasonable combination of the two, and this is the impression given to the couple. The couple prognosis is decided by the lowest grade assigned to a member, that is: wife good, husband poor, couple poor.

Using this system of grading we discovered that only 58 couples had a good prognosis (*Fig.*

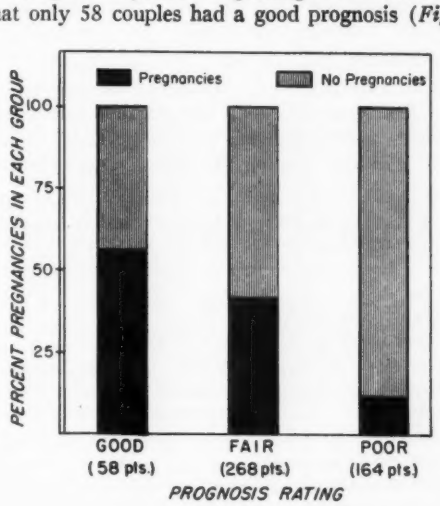

Fig. 9

Correlation of prognosis of couple at final conference with pregnancy results.

9). Thirty-three or 57 per cent subsequently had children. We think that this figure is probably higher, but we were unable to obtain any follow-up on some of these patients, especially those seen during World War II. Two hundred and sixty-eight couples were given a fair prognosis. In this group, 114 or 42.1 per cent of the wives became pregnant. In the poor prognosis group of 164 couples, only 20 wives or 12.2 per cent became pregnant. We were unable to estimate the prognosis in ten couples due to equivocal data. Four pregnancies occurred in this group.

It becomes evident that after completion of the survey and a fair evaluation of the study results, one can give the couple a rather accurate impression of their particular pregnancy expectancy. We do not give a "hopeless" prognosis. At times we have held this view privately and, on occasions, we have been surprised.

INTERVAL BETWEEN SURVEY AND CONCEPTION: PREGNANCY RESULTS

In order to give more intelligent information concerning how soon our couples may expect results we analyzed our data for the interval between completion of survey and pregnancy (*Table 4*). Seventy-eight pregnancies or 43.2 per cent had their inception before the final conference. Twenty-eight additional gestations occurred within two months of survey completion, 13 (7.6 per cent) from two to four months after survey, and 16 (9.4 per cent) from four to 6 months following the survey. During the next six months only 16 additional pregnancies occurred (9.4 per cent). Thus, during and within the first year following the survey, 143 pregnancies were conceived, or 83.6 per cent of the total number. During the second year only ten pregnancies had their beginning (5.8 per cent), and during the third year following survey only five (2.9 per cent). After three years, a total of 11 pregnancies occurred (6.4 per cent). These were spread over several years (obviously little influenced by our survey). We could not date the onset of pregnancy in two patients (1.2 per cent).

CORRELATION OF THE 171 PREGNANCIES AS RELATED TO INTERVAL BETWEEN SURVEY AND CONCEPTION

Time	Per Cent	
During survey	43.2	83.6 first year
Following survey		
2 months	14.0	
4 months	7.6	
6 months	9.4	
7-12 months	9.4	
13-24 months	5.8	
25-36 months	2.9	
Over 36 months	6.4	
Unknown	1.2	

Table 4

This information is of value to us in our final conference. We now tell the couple that almost 84 per cent of pregnancies occur during the first year, and recommend that those with a fair or good prognosis be rechecked in one year if no pregnancy occurs. We believe that those with a poor prognosis should certainly be encouraged to adopt a child following a year's trial.

SUMMARY

An analysis of pregnancy results is given for 500 unselected completely studied infertility couples. One hundred and seventy-one wives became pregnant during or following the survey. For less than one year of presumed sterility, the per cent pregnancy is 14.2 above the survey pregnancy per cent. There is a progressive decline but still positive deviation through three to four years. After this the deviation becomes significantly negative and remains so.

Husbands with a history of previous genital operations or significant abnormalities as varicocele, chronic prostatitis, and so forth, have a lessened incidence of paternity.

Obesity, underweight, hypothyroidism and hypometabolism in the husband do not appreciably alter survey pregnancy per cent. Obesity in the wife is associated with a minus 10.6 deviation and underweight a plus 7.8 deviation from the survey pregnancy per cent. There is a slight pregnancy increase in wives with hypometabolism or hypothyroidism.

Gynecologic operations were done in 205 wives prior to their survey. Dilatation and curettage, and myomectomy have a slight positive deviation. Cervical operations, uterine suspensions, ovarian and tubal operations, done elsewhere, show varying degrees of minus deviations.

Varying gynecologic diagnoses were made in 295 wives during the survey. Chronic cervicitis, retrodisplacement of the uterus and unilateral cystic ovary have a slight positive deviation from survey pregnancy per cent. Fibromyomata uteri, bilateral cystic ovaries, endometriosis, unilateral

and bilateral adnexal disease result in a minus deviation.

Estimations of prognosis were made at the termination of each survey. The prognosis and related per cent pregnancy are as follows: good, 57 per cent; fair, 42.1 per cent; poor, 12.2 per cent.

Eighty-four per cent of the total pregnancies occurred during or within the first year of survey completion.

CONCLUSIONS

(1) Detailed and careful infertility studies are justified after one year of sterile mating.

(2) The longer the duration of presumed sterility the less is the chance for pregnancy.

(3) Women have far too many operative procedures for the purpose of relieving infertility.

(4) Those couples with a poor, and possibly those with a fair, prognosis should seriously consider adoption if pregnancy does not occur within one year after termination of survey.

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DISCUSSION (*Abstract*)

Dr. Simon V. Ward, New Orleans, La.—A look at the urological history of the husbands in this series reveals several interesting facts. Varicoceles, unilateral cryptorchidism (with or without operation), and to a lesser extent, hydroceles, are associated with a rather marked decrease in the number of pregnancies accomplished. This will certainly make one scrutinize these findings and correlate these data more closely in the future. Dr. Davis' series would indicate that any condition affecting the blood supply to the testicles (even hernioplasty) has considerable influence in decreasing fatherhood, apparently even more influence than previous infection with the gonococcus.

As for findings in the wives, it is easily understood why, in cases of such a correctable condition as hypometabolism, the percentage of pregnancies accomplished was relatively increased. On the other hand, it is surprising that, even after cautery, patients with chronic cervicitis failed to show any appreciable increase in the achievement of pregnancy. One would have expected cautery to give more strikingly beneficial results.

It is gratifying to know that, in general, previous gynecological surgery did not even further lower the percentage of pregnancies accomplished. In fact, considering the previously existing disease for which in nearly half of the series surgery was indicated, I am surprised that there was not a lower incidence of pregnancy among women who had undergone such operative procedures.

Endometriosis, a classical cause of relative sterility, was found to lower the favorable outcome only to 26.1 per cent. I find this encouraging. Here, again, it would be interesting to correlate treatment. The 35 per cent incidence of pregnancy in women with retroversion varies only 0.8 per cent from the general average, bearing out the thesis that this gynecologic factor has little effect on a woman's ability to conceive.

In hearing this report, with its history of how the various conditions affected the outcome, I kept looking for the "silent group," those patients in whom no evident barrier to conception could be found, at least, nothing more drastic than too frequent coitus, postcoital douching, or the use of contraceptive jelly as a lubricant. We all know the couples in whom no abnormality is detectable and therefore no definitive treatment is possible. Their persistent failure to accomplish pregnancy, despite correction of coital habits and use of vitamin E or perhaps thyroid, presents us with some of our most baffling problems. In the authors' series, I suppose these are predominantly to be found among the 58 couples with a "good prognosis," since 57 per cent of these subsequently had children.

Forty-three per cent of all the pregnancies accomplished occurred during the survey, a startling report at first glance. However, this is the time during which bad habits were remedied and most of the treatment took place. It would be interesting to know how long the period of each survey averages.

The earlier work of the Durham group has provided a basis for minimal standards of sterility study. A similar though smaller study in our private clinic, based on the same standard of investigation as described by Hamblen, shows comparable results. In our series of 256 couples (half the number of the authors' series), 88 pregnancies resulted, an incidence of 34.3 per cent, almost identical with their 34.2 per cent.

The authors noted the fact that 83.6 per cent of all those who became pregnant did so during the study or in the ensuing year. Certainly this fact alone will help in prognosticating to the couple and in advising them concerning adoption.

Dr. Turner (closing).—Dr. Ward asked how we estimate the prognosis of the couple. The good couple was the couple in whom we could find no major factors responsible for the infertility. We did not consider hypometabolism or hypothyroidism as major factors. We think they are correctable.

The fair couple was one in whom there was some tubal factor present but not bilateral tubal occlusion, that is one tube blocked, or perhaps an estrogenic endometrium on several biopsies. This is a factor which can be corrected in some instances. There was usually slight to moderate seminal inadequacy present in the husbands.

The poor couple was the couple in whom the husband

had either aspermia or severe seminal inadequacy, or the wife a bilateral tubal occlusion or some other major anomaly.

We never give our couples a hopeless prognosis. On occasions we have been surprised when we held this view privately. As to the time of the completion of the survey, this varied anywhere from three to eight or ten months, depending on whether certain examinations had to be repeated. Many of our couples come from a long distance and it was not convenient for them to come month after month, so that sometimes they would wait two or three months before returning. Most of the pregnancies which occurred during the survey we felt could be attributed to the tubal test, as there is no other therapeutic measure during the survey which could achieve as much as that one measure.

We have planned a paper on therapy later, and for that reason we said nothing about it in this paper.

HIGH FLUID INTAKE IN THE TREATMENT OF ECLAMPSIA*

A REPORT OF 25 CASES

By FRANK E. WHITACRE, M.D.
and
OLIVER DELOZIER, M.D.
Memphis, Tennessee

The purpose of this brief report is not to discuss the controversial issues concerning the etiology of eclampsia or to redescribe the well known pathology, but rather to describe a method of treatment.

The obstetric staff of the John Gaston Hospital in Memphis is faced almost daily with the necessity of treating the severe toxemias of late pregnancy, and for some years we have directed a principal interest toward trying to understand these entities and improve methods for their management. In the years recently past, considerable attention was given to the development and utilization of technics of regional nerve block and to the study of the mechanism of their favorable effects and the control of unfavorable effects. This report of the use of large volumes of water in the severest toxemias, we believe to be far-reaching in its implications and perhaps valuable as present day methods of treatment are modified. The practice has for us simplified treatment and produced excellent clinical results.

These facts of simplicity of treatment and excellence of response to a regimen unlike that previously used at this institution were to us of sufficient importance to warrant this report. In an unreported series of 102 eclamptic patients treated by us from November 15, 1945, to January 15, 1950, by the modified combined method of Dieckmann[1] and regional nerve block, there were only three hospital deaths and one death attributable to the toxemia in the puerperal period. We do not mean to say that we consider this mortality rate of somewhat less than 4 per cent to represent an irreducible minimum, but we do recognize, as does anyone who sees a large number of these patients, that an occasional one will be so seriously compromised by her illness at the time when first seen that any treatment whatever will be unavailing. It was, then, the ease of handling and fast recovery of these patients following the use of large volumes of isotonic fluid which has impressed us.

Material.—This series of twenty-five cases of eclampsia was treated on the obstetric service of the John Gaston Hospital from January 15, 1950, to August 1, 1950. During this same interval there was a total of 2,130 deliveries on the inpatient service. The incidence of eclampsia, considering this group alone, was 1.17 per cent; but as is true of many metropolitan maternities, a large part of this group consisted of patients sent in for treatment from outlying areas within a hundred-mile radius of Memphis.

Twenty of the group of twenty-five patients were primigravidas with an average age of 16.6 years. Of the five multiparas of average age 24.8 years, only one had had eclampsia previously. These figures agree in general with the incidence as to age and parity reported by many other observers, and we have no reason to believe that this group differed materially in any respect at the time of admission from the larger group previously treated at this institution. Included in this group is every patient seen on the service who had a convulsion in late pregnancy at a time when she exhibited any signs or symptoms of toxemia. The only patient who had a convulsion and was not included was a known epileptic patient followed in the outpatient department who did not at any time during the pregnancy demonstrate any evidence of preeclampsia.

TREATMENT

We have at the John Gaston Hospital followed the widely accepted principle of controlling the eclampsia prior to interruption of the pregnancy.

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*Read in Section on Obstetrics, Southern Medical Association, Forty-Fourth Annual Meeting, St. Louis, Missouri, November 13-16, 1950.

*From the Division of Obstetrics and Gynecology of The University of Tennessee College of Medicine, Memphis, Tennessee.

It is in this medical handling that we believe an advance has been made. We have used no diuretic agents other than water in this series, and we have learned how to use it with safety for its excellent diuretic effect. This represents an employment of the method suggested by McPhail,[2] previously, judging from the literature, not much used.

McPhail noted in his original and subsequent articles a fact which most of us have observed, namely, that eclamptic patients exhibit signs and symptoms strongly indicative of dehydration. Their skin and mucous membranes are dry; their urine is scant and highly concentrated; their respiratory secretions are thick and tenacious; their hemoconcentration is evidenced by elevated hematocrit values; their first request upon regaining consciousness often is for a drink of water; and their consumption of water, if it is made available, frequently ranges up to five to eight liters within a twenty-four-hour period.

These facts being true, it is perhaps surprising that more effort has not been directed toward the supplying of sufficient amounts of water for the correction of the dehydration. It is, on the other hand, understandable that there should be reluctance about the administration of large quantities of fluid to an individual already edematous. We have found that concern about the possible ill effects of such therapy was unfounded, and that water in considerable volume may with proper safeguards be used not only with impunity, but with consistent benefit.

Successful care of eclamptic patients is necessarily alert, intensive, and highly individualized. At our hospital these patients are the recipients of considerable attention from visiting, house, and nursing staffs. During their critical period their treatment is constantly supervised by a member of the resident staff. The regimen of treatment followed in general is outlined below:

(1) Glucose, 5 per cent, in distilled water, 1,000 cc., intravenously, every 6 hours through a Murphy drip at 60 drops per minute.

(2) Elevate the head of the bed 18 inches.

(3) Initial sedation, sodium amytal, grains 3¾ to 7½, intravenous.

(4) Subsequent sedation, sodium phenobarbital, grains 3, intramuscular, every 6 hours.

(5) Oxygen, 6 liters per minute by nasal catheter.

(6) Penicillin, aqueous, 100,000 U. every 3 hours, intramuscularly if the patient is comatose or febrile or if the membranes are ruptured.

(7) Turn the patient every hour until conscious.

(8) Insert an indwelling catheter.

(9) Measure intake and output and record every 6 hours.

(10) Record every 15 to 30 minutes blood pressure, pulse, pulmonary edema if present, fetal heart tones, and uterine contractions.

(11) Draw blood for carbon dioxide combining power, nonprotein nitrogen, total and fractional proteins, packed corpuscular volume, type, and crossmatch.

(12) In severe cases only, if the blood pressure fails to stabilize at levels lower than those on admission in 4 to 6 hours, continuous regional block is instituted in order to reduce the blood pressure and make intracranial hemorrhage and severe pulmonary edema less likely.

(13) Whenever the pulse exceeds 120 per minute without temperature elevation to account for it, the patient is to be digitalized.

(14) When the eclampsia is well controlled, usually less than 48 hours after admission, a vaginal examination is done and plans are made to empty the uterus by the most conservative means.

(15) When the patient is rational, a low sodium acid-ash diet is offered and plain water by mouth urged to 6,000 cc. daily, the intravenous infusions being discontinued as this intake becomes possible.

(16) No ergotrate, stilbestrol, or ice caps are used during or after delivery. Pitocin is used at cesarean section.

(17) If sedation other than the barbiturates is needed, magnesium sulfate, 50 per cent solution, 4.0 cc. intramuscularly every 4 hours for six administrations may be used.

Our experience in the use of intravenous fluids in treating eclamptic patients as we did formerly was such as to make us share the concern voiced by Mengert and Hermes[3] that their vascular systems might be overloaded. It was not at all uncommon, for example, to find significant pulmonary edema in a patient previously apparently well compensated following the administration of 20 per cent glucose or plasma. Theoretically desirable though we believed it to be, we approached the giving of large quantities of isotonic glucose with some apprehension. Our fears were unfounded. Not only have we failed to cause pulmonary edema by such infusions, but we have proceeded with them in the face of pre-existing edema with no apparent ill effects and with progressive clinical improvement. Let us emphasize the fact that the flow is very slow, one liter requiring from four to six hours. It will be clear from the outline above that just as soon as the patient is rational and able to take fluids by mouth, water is substituted in large volume for the intravenous fluids first given.

To prevent a shift in already present edema fluid from its harmless location in the extremities

to the abdominal cavity and thorax, the head of the patient's bed is elevated eighteen inches, the figure being the one suggested by Dock[4] in the handling of patients with congestive heart failure.

We have relied on the barbiturates almost altogether for required sedation. The dosages noted above are those usually employed for a period of about twenty-four hours. We have found that as soon as the patient is well hydrated, she will, if not in labor, rest quietly on sedation as little as two to three grains of phenobarbital per twenty-four hours. Long before the theoretical disadvantages of morphine were pointed out by Brown and his co-workers,[5] we had abandoned its use as unnecessary.

We use penicillin liberally as prophylaxis against pulmonary and intra-uterine infection, the latter effect giving us a freer hand in deciding upon the time and method of termination of the pregnancy.

Delivery is not, however, usually postponed much longer than forty-eight hours after admission. At or before this time a vaginal examination is done. If the cervix is favorable, pitocin induction is attempted. If found to be unfavorable and normal delivery is not to be expected in the foreseeable future, cesarean section under regional anesthesia is practiced. We avoid committing an eclamptic patient to a long hard labor against a firm cervix. Our cesarean section rate is 18 to 20 per cent.

RESULTS

All of this group of twenty-five patients survived, a fact which we noted to be little improvement in mortality rate over that of a larger group treated by us, using another regimen. It was the prompt and consistent improvement obtained and the ease of handling of patients who became reasonably lucid and cooperative within twenty-four to seventy-two hours that have favorably impressed us. A number of facts concerning them are worth noting:

(1) While there was occasionally a visible increase in gross edema during the first few hours of treatment, this was followed by diuresis, often reaching considerable proportions. Clinical improvement occurred along with the initial increase in edema and continued with the clearing of edema which proceeded rapidly, usually being complete by the third or fourth day postpartum.

(2) The moderate to high fevers sometimes seen as a part of the picture of severe eclampsia did not occur in the absence of infection in the patients in this series.

(3) Respiratory secretions became and stayed fluid and easily manageable by the patient. Obstruction of the airways was less frequent and the need for mechanical suction less common than formerly.

Notable, too, was the low fetal mortality. Of the twenty-seven infants born to twenty-five mothers, twenty-three survived and were discharged from the hospital in good condition. This gross fetal salvage rate of 85.18 per cent does not, however, tell the whole story. Of the four infants lost, two were known to be dead from the time of admission, macerated fetuses being delivered vaginally in each case. The two others were fetuses delivered electively by abdominal hysterotomy at twenty-seven and twenty-nine weeks, respectively, following eclampsia of the early third trimester. Every other fetus survived.

It was interesting to observe that these infants were, in general, born in better condition than those delivered before institution of the present treatment. This fact we attribute to the improved maternal and fetal physiology and to the decreased maternal requirement for depressant drugs.

ILLUSTRATIVE CASE REPORTS

An 18-year-old colored primigravida was sent into John Gaston Hospital by her physician. A history was obtained of dependent edema for one month, severe headaches for two days, and four generalized convulsions beginning at 3:00 a.m. of the morning of admission. She was found to have considerable generalized edema, blood pressure of 145/110, and 3+ proteinuria. The fundus of the uterus was at eight months, contracting regularly at three-minute intervals. Routine eclampsia therapy was begun. After two hours of labor she was delivered of a normal, living, colored female under saddle-block anesthesia. With an intravenous fluid intake of 4,000 cc. per twenty-four hours, the patient within twelve hours experienced a diuresis at the rate of 3,800 cc. per twenty-four hours. Recovery was rapid. The patient was discharged on the tenth hospital day asymptomatic with a blood pressure of 136/80.

A 15-year-old colored primigravida was admitted on March 12, 1950, at 8½ months' gestation following six generalized convulsions during the preceding four hours. She was found to have a blood pressure of 130/100, 1+ dependent edema, and a 3+ proteinuria. Routine eclampsia therapy was begun. During the first eighteen hours her total output was 145 cc. with 3,000 cc. intake; but following this it was for six-hour intervals 100 cc., 175 cc., 210 cc., 410 cc., and 500 cc., respectively, in the face of intake of 1,000 cc. for each 6-hour period. Though there was visible increase in edema, the patient's general condition improved. Prophylactic digitalization

was done. Low cervical cesarean section was performed under continuous caudal anesthesia on the third hospital day with delivery of a normal colored male. A tremendous diuresis followed, the output during the next twenty-four hours totalling 5,800 cc. The patient improved rapidly and was discharged on the twelfth hospital day, asymptomatic, with a blood pressure of 120/80.

A 16-year-old primigravida was admitted on June 26, 1950, at term but not in labor. The blood pressure was 140/90; and she evidenced 3+ proteinuria and 1+ edema. She was known to have a borderline contracted pelvis. A few hours later the patient experienced a severe generalized convulsion. Intensive routine treatment was started, and after twenty-two hours, a low cervical cesarean section was done under continuous spinal anesthesia with delivery of a normal, living, colored, male infant. The urinary output rose from 500 cc. in the twenty-four hours immediately antepartum to 4,875 cc., 5,300 cc., and 5,900 cc. on successive days. Recovery was rapid. The patient was discharged on the eleventh hospital day asymptomatic with a blood pressure of 110/80.

SUMMARY

(1) An account is presented of the treatment of twenty-five eclamptic patients, all of whom survived.

(2) The treatment used was simple of execution and productive of prompt clinical improvement.

(3) A principal feature of it was the use of infusions of large amounts of isotonic glucose, a procedure which with proper safeguards was found to be benign.

(4) Twenty-three of twenty-seven children survived, the four lost including two dead on admission and two barely viable.

(5) The simplicity and apparent effectiveness of the treatment used suggests that it might be widely applied with an increase in maternal and fetal survival.

(6) A previous series of 102 eclamptic patients treated by another regimen has been mentioned. This series of 25 eclamptic patients treated with a high fluid intake as a part of their management is herein reported. This should be considered as a preliminary report, and when a sufficient number of patients has been treated the results will be compared with the previous series.

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DISCUSSION (*Abstract*)

Dr. Willis E. Brown, Little Rock, Ark.—Over a year ago I moved to the eclampsia belt, where I have had an opportunity to see at first hand what you men have been seeing for many years, and I think the arguments *pro* and *con* regarding the management of eclampsia are really arguments of difference in perspective.

Physicians who have had their training and experience entirely in the North have little concept of the problem which faces those of us who practice in the South. As a member of the Southern group I have seen at first hand in the last 15 months 29 eclamptics in many respects identical to the group which has been reported from Tennessee.

In this disease about which we know little we focus our attention upon the symptoms which are obvious. One group of investigators concentrates its attention upon the hypertension, another upon the edema, and a third upon protein metabolism and albuminuria. As long as we know little about the etiology, we shall probably continue to do this.

The series of cases reported is of interest because Dr. Whitacre is focusing his attention upon edema and water balance. We recently delivered 23 consecutive eclamptic patients without a death. However, our next six eclamptic patients provided us with two deaths; so among 29 patients we have had two deaths.

One of these patients died of profound pulmonary edema which developed within six hours after admission. She was dead in 18 hours. I seriously doubt whether intravenous 5 per cent glucose or any other regimen of therapy would have had a significant effect upon her outcome.

I should like to review very briefly with you the history of the theories upon water metabolism in the management of eclampsia. The obvious edema led our forebearers at the turn of the century to deprive these patients of water. We went through an era known usually as the dehydration era, in which they were given no fluids by mouth or by vein.

Following the work of Dr. Newburg, the group at Ann Arbor entered upon a schedule of forced hydration, water in amounts of four, six to eight thousand cc. per day, and many patients were drowned.

Lately we have turned from these two extremes. Now two or three thousand cc. of fluids are given per day, and the concept that the increase in electrolytes or colloids within the fluid may be advantageous has developed.

Under the leadership chiefly of Dr. Dieckman, 20 to 30 per cent glucose has been given intravenously. Some years ago my associates and I reported a number of experiments showing that hypertonic fluids were not only of no value, but were actually antidiuretic in their effect upon the pituitary.

The series of cases reported from the University of Tennessee is of interest. They are doing three things: (1) they have discontinued hypertonic glucose; (2) they are increasing the use of cesarean section by 20 per cent; and, (3) they are adding isotonic fluids.

It is difficult to say which of these three procedures has resulted in their apparent improvement in manage-

ment. I would venture to guess that it is not so much the use of isotonic fluids as it is the discontinuance of hypertonic fluids. We shall all watch for the final report from this clinic with great interest.

I would caution, however, against returning either to the extreme of drowning or to the extreme of profound dehydration. Perhaps all we need do is to stop giving hypertonic glucose.

Dr. Richard Paddock, St. Louis, Mo.—Over a period of years comparable to those years of the experience of Dr. Whitacre, we have all seen various methods used in the treatment of severe eclampsia; the Strogonoff method, the marked reduction or restriction of fluid intake, the bleeding of the severe case, the administration of magnesium sulfate, regional nerve block, and numerous combinations of these measures. All have possessed certain advantages at the time they were in vogue. As the author says, "An occasional one will be so seriously compromised by her illness at the time when first seen that any treatment whatsoever will be unavailing." These are the cases that give us our irreducible mortality figures regardless of the method of treatment employed.

It would seem that if improvement follows this method of treatment as rapidly as is anticipated, delivery could be postponed for longer than 48 hours after admission, or as long as improvement continued. This would place the patient in better condition for delivery by the method of choice.

The fetal salvage results in this series are much better than one would ordinarily expect and speak highly for the method.

In the cases reported the blood pressure was much lower than that in most cases of severe eclampsia that I have seen. This may be accounted for because of the early age of the patients.

Dr. William M. Howdon, Miami, Fla.—We at the Jackson Memorial Hospital in Miami have been extremely interested in this subject for the past ten years, have spent considerable time and money upon it, and have surveyed more than 200 eclamptics.

Today, backed by the Medical Research Foundation of Dade County, we are determining the fluid, electrolyte, and nutritional balance, as well as some hormonal balances, in the eclamptic. Of the three programs of treatment which have been instituted: (1) Rotunda (morphine sulfate, venesection, starvation, et cetera; (2) Temple (dehydration by sprinal taps, hypertonic glucose, et cetera; and (3) Veratrine (dilates the arterioles, depresses the cardia, causes nausea and vomiting, decreases urine volume, produces shock). It is today easy to see why there are objections to each. One of the encouraging things about the program this morning is that veratrine was not mentioned. We feel that veratrine is contraindicated and, specifically, it is anti-physiologic. The eclamptic manifests all of the findings of one suffering from hematogenic shock, namely: a decrease in circulating blood volume, acidosis, a decrease in vascular capacity, and hemoconcentration. These points can easily be shown by studies of the carbon dioxide combining power, serial hematocrit and blood volume studies.

So, instead of venesections, spinal taps, and depressent drugs such as morphine sulfate, and water with varying concentrations of glucose, we have made an effort to re-establish a normal circulating blood volume by giving the most physiologic solution of all, namely, whole blood and concentrated plasma. If the latter is not available, normal liquid plasma may be substituted. The arteriolar spasm we relieve with magnesium sulfate and sedation (intravenous pentobarbital sodium) and other medication that is not specifically contraindicated. Beyond question, it is more physiological to supply whole blood and human plasma than water or saline, with or without glucose. Electrolytes or crystalloids cannot replace colloids in restoring or maintaining intravascular osmotic pressure.

Avoid the subcutaneous or intramuscular route of administering such medication as barbituric acid derivatives and digitalis, because, following the giving of whole blood and plasma, the colloidal osmotic pressure will be raised and there will be clearing of the interstitial spaces of edema fluid and, with this, the depot of medication will be cleared and will produce in some a variable degree of neurogenic shock. Then one is confronted with treating a patient with simultaneous neurogenic and hematogenic shock.

In our studies, we feel that the major cause of "true eclampsia" is nutritional. When one studies closely, all patients with eclampsia show signs of nutritional deficiency. Diet is not the all important factor, but the supply, absorption, and utilization of all minerals, vitamins, and proteins in relationship to the demand. For example, vitamin B_6, pyridoxine hydrochloride, is of considerable importance. If one is deprived of vitamin B_6, albuminuria will develop; there is also an elevation in blood uric acid and a decrease in urinary uric acid. A deficiency of B_6 prevents the essential amino acid tryptophane from forming nicotinic acid. We do not think that an elevated blood uric acid is of any importance as far as diagnosis or prognosis in the eclamptic is concerned. Most laboratories today use phosphotungstic acid in making uric acid determinations to which a number of compounds (sulfhydryl) react. The uricase test is the only one I know of which is specific in determining uric acid; however, it is expensive and time-consuming. Other vitamins and minerals are of equal importance but time does not permit further discussion.

We stopped giving morphine sulfate about twelve years ago for a number of reasons. It increases acidosis (decreases carbon dioxide combining power), increases hemoconcentration, decreases the plasma volume flow through the kidney, increases renal re-absorption, increases intracranial pressure, increases lactic acid, decreases liver function, and increases the respiratory center threshold to carbon dioxide stimulation, thereby decreasing respirations. All of these effects are the reverse of what we should like to accomplish.

We think that there is a place for cortisone and ACTH in the emergency treatment of some eclamptics, and we hope to report upon this in the near future.

Dr. Stanley T. Garber, Cincinnati, Ohio.—It is with pleasure that we note the limited use of spinal anesthesia by the authors in the management of eclampsia. With the other methods used, we at the Cincinnati General Hospital are very much in accord. We have used unrestricted fluids for over 20 years. For a while we used 10 and 20 per cent hypertonic glucose, but for the past

five or six years we have used only 5 per cent glucose in water, as the authors noted. We feel that water is a most effective diuretic agent.

We have not used sedatives other than magnesium sulfate. We can only suggest that the authors try the veratrum alkaloids in their intravenous fluids to relieve the abnormal vasopressor activity of eclampsia, to improve the circulation and secondarily to lower the blood pressure. It is very simple, more predictable in the results accomplished, and safer than spinal anesthesia.

We now have had in over 20 years, more than 200 consecutive eclamptic patients treated with the veratrum alkaloids. There were 3 deaths, a gross maternal mortality of less than 1.5 per cent. Two patients, poorly handled in the early years of this series, died of sepsis following delivery. One patient died of eclampsia *per se*, a corrected maternal mortality of less than 0.5 per cent.

Dr. DeLozier (closing.)—The questions raised here have been for the most part taken up with the resident staff often enough by Dr. Whitacre so that I believe I can answer them much as he would.

As for the matter of drowning the eclamptic patients with the administration of large quantities of fluids, I can answer only that it has not occurred in our experience because of slow administration of fluids and proper supportive measures to the heart when indicated. We have administered intravenous fluids to this group of patients in the volumes reported, and occasionally as much as 7 to 8 liters per day by mouth, and we have not encountered pulmonary edema as a result.

The cesarean section rate among eclamptic patients at the John Gaston Hospital has remained practically the same over a number of years. At the time when the regimen of hypertonic glucose and continuous spinal anesthesia was being used, our patients were still being delivered by cesarean section at the rate of about 20 per cent. We do not feel that the improvement in maternal and fetal mortality is a reflection of any change along that line. We do feel that these patients, at the time of their admission on our service, are dehydrated, and that a volume of fluids sufficient only to replace their insensible loss, plus their daily urinary output, would be insufficient to correct the dehydration and therefore we should expect little improvement if that volume only were supplied.

Dr. Paddock raises the question about the interruption of the pregnancy at the end of 48 hours, or a period approximately as great, while the patients are still improving. Very recently, as our experience with the use of high fluid intake has increased and as we have been convinced of the safety of allowing the pregnancy to continue, we have begun to allow patients to remain pregnant longer than 48 hours. Two patients of the last ten were allowed to maintain their pregnancy for periods of seven and ten days respectively, at the end of which time they went into labor spontaneously and delivered uneventfully. It is probable that as our experience further increases, we shall find that we can maintain patients for considerable periods of time on the plan of treatment outlined, allowing them to deliver at a time when, as Dr. Paddock notes, they will be further improved.

It has been suggested that the patients presented were probably mild eclamptics because of the low blood pressure recordings made on admission. These patients were seen soon after their first convulsions occurred when, as most of you know, the blood pressures are likely to be quite low in comparison with former levels. Blood pressures of these patients went to the levels of 160 to 200 systolic that we have all learned to expect in this group.

Spinal anesthesia has been less used than it was formerly. We still use continuous spinal, or continuous caudal anesthesia, to lower the blood pressure and to control the pain of uterine contractions. In brief, we use spinal anesthesia for those patients whose blood pressure does not respond to drug therapy.

THE TWO-YEAR SCHOOL IN MODERN MEDICAL EDUCATION*

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(A) PRESENT STATUS OF TWO-YEAR SCHOOLS

Between 1900 and 1915, ten of our present medical schools organized, or reduced their curricula to, two-year schools. In 1940, there were still ten two-year schools (Alabama started in 1920; Wisconsin went to four years in 1925). Utah, Wake Forest, and Alabama established four-year programs during the past decade. Of the seven present schools of basic medical science, North Carolina and Mississippi are actually at work converting to four years, Missouri and West Virginia are continuing an active study of plans for four-year schools, as is North Dakota. South Dakota and Dartmouth apparently do not contemplate a change soon. We see then, that nearly all the two-year schools originated during the first fifteen years of this century and nearly all are disappearing during the fifteen years beginning with 1940. Undoubtedly many factors influence these developments, including demands for physicians, economic considerations, and evolution of the medical curriculum. Certainly a major factor in the continuation of these two-year schools during the first part of the century was the setting up of the basic science curriculum as a distinct two-year unit, referred to until recently as the "preclinical" portion of medical education.

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The term "preclinical" is replaced now by the more apt term "basic sciences," which go hand in hand with clinical medicine throughout the career of the modern physician. That we are now in an important transition period in medical education is a matter of general agreement. It is reflected for example in the care with which the Survey of Medical Education stresses its function as a "survey" and not an "evaluation." Our standards of evaluation have rapidly lost their rigidity, in these years of rapid change. I would not presume, therefore, to speak with any degree of certainty on the subject of the role of the two-year school, but would hope only to mention a few factors which seem to be of importance in considering this question.

(B) GENERAL TRENDS AND CONDITIONS OF SIGNIFICANCE

(1) *The Increasing Responsibilities of Medical Schools.* — The responsibilities of the modern medical school go far beyond the four-year educational program for undergraduate students. Responsibilities have increased rapidly in the relationship between the medical faculty and hospitals, not only for educational programs but for leadership in offering high quality medical services. Typical of this trend is the development in the Veterans Administration Hospitals. The increasing emphasis of various specialty boards on training in the basic sciences is a definite factor in this increased load on medical faculties.

Any medical school that is to serve as an effective center for continuing medical education and for strengthening the teaching programs of small hospitals within its area of influence, must have a strong clinical faculty. The school which remains a two-year school will not be able to assume its responsibilities in these important areas of modern medical school activity.

The tax-supported medical care programs which are developing rapidly in many states call for some advisory body to which that state can look, and which will be as objective as possible in contributing to long-range planning. Our society has not yet developed any group more adequate than a medical faculty for helping in this complex task. This represents a definite responsibility for the modern clinical faculty. Obviously, clinicians are needed.

(2) *Internal Changes in the Medical Curriculum.*—Following the reforms in medical education of the first and second decades of this century, the medical curriculum became so fixed that there was a clear line drawn between the basic science years and the clinical years in the medical school program. There is obvious now an increasing tendency to place more and more clinical activity in the first two years of work. For example, several schools have combined into a single sophomore course part of the neurology from the junior year, the neuro-anatomy from the freshman year, and that portion of physiology dealing with neurology.

Many such instances mark the disappearance of the sharp line of demarcation between the first two years and the last two years of the four-year program. With the disappearance of this sharp line, it becomes increasingly difficult for a two-year school to interdigitate its curriculum with that of another school.

The rigidity of the medical school programs of the first half of this century is somewhat incompatible with the changing scene in American medicine. More and more schools will undoubtedly undertake large scale curriculum revisions, such for example as the study and experiment now beginning at Western Reserve. This will make it increasingly difficult for a two-year school to coordinate its program with more than one or two, or at the most several, of the medical schools if they are all experimenting in slightly different ways.

(3) *The Financial Problem.* — The financial crisis in medical education is constantly before us. University presidents have become increasingly aware of the unusually heavy burden which medical schools have thrown on total university budgets. Certain financial arrangements have particular significance for the two-year school, such as the arrangement West Virginia has had for some years with the Medical College of Virginia, or the arrangement for the payment of $1,500 by the state of Mississippi to those schools which take the graduates of its two-year school. The University of Colorado has instituted an arrangement for out-state payment, which enables it to take students from other states, if those states are willing to pay the actual cost of medical education.

It is fair to guess that some arrangement for payment for the cost of the last two years' work will have to be made by those states that continue with two-year programs.

(4) *Demand for More Physicians and Increased Medical School Enrollments.*—The generalized demand for more physicians has been one

of the major factors leading to increased enrollment in medical schools. The 7,042 students entering medical schools in 1950 represent a 17 per cent increase over the average number of freshmen in the ten years preceding World War II. Several states are planning to build new schools. Most schools that can possibly do so have been increasing the number of students taken into freshman classes. In some schools the bottleneck has been in the laboratory space or in the instructional staff for the basic science courses, and in other instances the bottleneck has been in clinical facilities for the education of juniors and seniors.

(C) PROBLEMS FACING A CONTINUING TWO-YEAR SCHOOL

(1) The transfer problem is the most pressing, despite the present high quality of available students. Several trends furnish grounds for optimism: the increasing enrollment in medical schools, and the decreasing number of schools of basic science, will result in a fewer number of total students to be transferred, and a larger total medical school capacity. The increasing number of medical school affiliations with hospitals is increasing the student capacity at clinical teaching levels.

These factors, however, are probably more than offset by such factors as the following, which are making it increasingly difficult to transfer students.

(a) The rapidly increasing diversity of medical curricula in the various schools makes it increasingly difficult to interdigitate the study program of the two-year schools with many of the schools to which students have formerly transferred.

(b) Fewer students are failing, and therefore, many places available formerly due to attrition are no longer available.

(c) The pressures for increased enrollment have caused many medical schools to break the bottleneck of the limitation of numbers in the basic science courses and increase the number of incoming students. In some schools, therefore, within a year or two, this increase in the size of the freshman class will be reflected in a smaller number of available places in the junior year for transfers from other schools.

(d) Problems of financing, and problems of state restrictions, will present increasing difficulties.

Arrangements for transfer could be made most effectively with sound long-range planning in the relationship between the schools involved. In the case of schools actively considering change to a four-year program this development of mutually satisfactory arrangements with other schools for transfer of the students is made difficult, due to the uncertainty as to the timing of the development of a four-year program.

(2) *Tension of Students Is a Major Problem.*—The tension on the student in the two-year school, who is in suspense regarding transfer, all too often goes far beyond that necessary to stimulate learning, and serves as a block to the learning process. The tension on the faculty to prepare students for numerous other schools results in internal pressures within the courses offered in the two-year school, which in turn tend to develop a degree of competition greater than in four-year schools, and probably unwholesome.

(3) *Limitation of Progress Due to Lack of Freedom for Experimentation Is a Problem for the Faculty.*—Constant pressure to fit their students for the programs of other schools tends to place the two-year school in the position of a second-rate contributor to progress in medical education.

(4) *Dependence on Arrangements with Other Schools Will Undoubtedly Continue to Increase.*—All these factors combine to support the conclusion that in the future the only satisfactory arrangement for a two-year school will probably be in the direction of more definite alignment of the program of the two-year schools with some specific four-year schools. These four-year schools would be drawn more and more into questions regarding selection of students and changes in the curriculum for the two-year school. The present trends make it appear that the freedom of the two-year schools will be increasingly limited, and in fact that their only opportunity for survival will be to depend upon some program which takes them under the wing of one or more existing four-year medical schools.

(D) FACTORS POSSIBLY CALLING FOR NEW FUNCTIONS OF TWO-YEAR SCHOOL

(1) *Recent Consideration for Establishing Two-Year Schools.*—Within the past few years considerations of the establishment of new schools of basic medical science, such as in the state of Arizona, and at one of the colleges in Southern Illinois, have led to the conclusion that such a move is unsound at present. No new two-year

school has been established in thirty years. It may be possible, however, that certain trends are at work which will call for the development of a new role for the two-year school in education for the health sciences, including medicine.

(2) *Trends That May Be Important.*—(a) Since the modern physician is only one member of a team of professional workers necessary for maintaining the health of the people, present trends are in the direction of increasing professional education of such groups as nurses, social workers, health educators, various technical personnel, and various public health workers. We face the task of re-examining, during the next few decades, the optimum division of labor among variously trained personnel if we are to render most efficiently the highest possible quality of medical care, and of health services to the people. It is conceivable that we may reach the stage where there would be a common core of subject matter which will be applicable not only in the training of the M.D., but in the educational program of a number of other health workers. While this trend may crystallize into some definite need for combined programs within the next few decades, it is unlikely that it will come about in less than twenty or thirty years.

(b) As we have mentioned, the medical school has a responsibility which goes on beyond the granting of the M.D. degree. It involves both hospital training programs and programs for continuation training of practicing physicians. Increasing demand for combining professional training with a general cultural education, in some instances may cause medical schools to take an interest in the student from the time he leaves high school, although at present this task is clearly delegated to the liberal arts college. The pressures brought about by the 12 to 14 years beyond high school necessary to become a physician may encourage trends at the professional school level similar to the development of the junior high school concept, and more recently the junior college concept. It is quite possible that within two or three decades we shall see the suggestion for a reallotment of time during this 12-year period, which permits closer relationship and administrative unity between the clinical years in medical school and the prolonged program of hospital training. This is more likely to occur when medical schools take over a more definite responsibility for all hospital training. This involves the question of the present role of the specialty boards in dominating the educational programs at this level, and is a question too complex to explore further here. It is conceivable that within a decade or two, as an outgrowth of these problems, the line between the work actually done in the first two years of medical school and that done later, will again become a more clear-cut line rather than the hazy boundary which it now appears to be.

Even admitting the possibility that both of these major trends will have some influence in increasing the importance of the role of the two-year medical school, it is hard to visualize the evolutionary processes developing at a speed which would cause these factors to be important in less than the next twenty-five years. It would, therefore, seem unwise for any two-year school to justify its continued existence as a two-year school because of these factors which are yet far off in the future.

(E) FACTORS NECESSARY FOR DEVELOPING A FOUR-YEAR SCHOOL

(1) *Finances.*—Financing the establishment of a four-year medical school is such a major problem that frequently it overshadows other factors just as important. The original cost of buildings for the physical plant is secondary in importance to the continuous operational budget. From the standpoint of the university the most important problem is how to assure an adequate operational budget for the medical school, without jeopardizing the financial support of other important and necessary university programs. Most universities which have a successful or outstanding medical school have found it necessary to face quite squarely the fact that in our present state of development it is necessary for the medical school to be considered as a special case, or in other words as a fair-haired boy in the university family. It is interesting and important to note that in the case of the three states which have moved ahead in developing four-year schools in the Southeastern area, (Alabama, North Carolina, and Mississippi), it has been necessary to educate the public and the legislative bodies in regard to the separate consideration of the financial underpinning of the medical school, as compared with the rest of the university. This calls for attitudes on the part of governing bodies and administrations of universities which set the medical school problem aside as one distinctly different from other divisions of the university.

(2) *Teamwork.*—As important as the financial aspects of the development of a four-year medical

school may be, these after all are secondary to the establishments of a spirit of faith and mutual confidence among those who control the various resources of the state. In every instance where a state supported school of basic medical science has developed into a four-year school, there has been a long history of years of effort put into developing an integrated approach, not only on the part of university officials, but of other agencies and groups in the state who are interested in health programs, including state health departments, physicians in the state, and the people in the state whose health is at stake.

Where this integrated approach has been developed it has been possible even for states with limited resources to move ahead on their medical programs.

(3) *The Problem Is Broader Than the University.*—Since many other important aspects of this problem are involved, it is important to realize that the consideration of the establishment of a medical school involves factors that go beyond the immediate interests of the university, and call for the cooperation of other state agencies and interests in the adoption of a long range plan.

(4) *Loyalty to a Common Goal Ahead of Controversy and Fixed Ideas.*—Wholesome difference of opinion is an asset up to a certain point, but when controversy becomes long standing, the fixed ideas of groups with vested interests becomes a handicap. People are very much alike, and there is just as much likelihood that there are vested interests in one group as in another. The important thing is that any state which foresees the need for developing a four-year medical school will never make progress unless loyalty to the needs of the state is put ahead of the vested interests of any groups. Importance must be placed first on the development of a program which utilizes the resources of the state to meet the needs of the state. Unless the emphasis is on this rather than on questions of location or of capital building expenses, it is unlikely that a sound medical program will develop.

SUMMARY AND CONCLUSIONS

The period of the two-year school in modern medical education may be thought of as being the years 1915 to 1940. Its successful contribution has been closely related to the two-year, self-contained unit of the basic sciences. Evolution in the medical curriculum is rapidly eliminating the distinct line separating the first two years from the last two years of the four-year program.

The increasing responsibilities of the modern medical school makes it essential to have a strong clinical faculty. The two-year school cannot meet fully the demands placed on the modern medical school.

Despite well-qualified students, the transfer problems of the two-year school are increasing because of (a) increasing diversity in the curriculum, (b) fewer failing students, (c) problems of financing and of state restrictions. The difficulty is only partly offset by the increasing capacity of all medical schools and the decreasing numbers of two-year schools. The increasing tension on students, and the limitations on the faculty of the two-year school, portend rapidly increasing dependence of each remaining two-year school on one or several four-year schools. The degree of dependency may well involve decreasing freedom of the two-year school in determining its own methods of progress.

The evolution in educational programs for various types of health workers, and a reallotment of time groupings for the long years required for medical education may bring changes which again would set out two distinct years of work that would stand as a unit. It can hardly be expected that these trends will justify conscious planning for continuing a modern medical school with only two years of work.

The development of a four-year school requires money but more important is a spirit of teamwork, mutual confidence and devotion to a common ideal on the part of various interested agencies and groups in a state, including the university.

In view of the need for the four-year program and in view of the difficulty of continuing the operation of the two-year school, there seems little or no justification for any state with adequate resources to delay in converting its school of basic medical sciences to a full medical school.

DISCUSSION (*Abstract*)

Dr. Robert A. Moore, St. Louis, Mo.—We at Washington University have been interested in the problem of the two-year medical school of necessity, because a significant fraction of the transfer of students we take in the third year, in all about twenty, come from the University of Missouri. We have watched the developments there with some interest because it would make a

great deal of difference in our junior year if the University of Missouri were to become a four-year school.

There is not much that I can add to what Dr. Stubbs has said except to emphasize some points. We have been impressed with this, that although we make a serious attempt to fit the curricula of two-year schools and four-year schools together and although we may make a serious attempt to acclimatize the students who transfer in the third year, the jump from one school with one philosophy and one educational program to another school with another philosophy and educational program in the middle of the program of medical education, puts the student in a difficult position. I do not think many of them are hurt seriously, but many are hurt to some degree. On that basis, I would agree with Dr. Stubbs that we cannot justify many more two-year schools, and we should try to change the two-year schools to four-year schools when that is physically and academically possible.

Dr. Stubbs also mentioned the increasing lack of separation of the so-called basic sciences and the clinical sciences. I do not quite know where pathology, my own subject, belongs. I should put it in the middle, having some on one side and some on the other side. I agree with the basic science teachers that we should be very careful that the clinical subjects do not encroach upon the time in the first two years.

Dr. Stubbs mentioned the possibility that medical schools may become responsible for all hospital training. I cannot resist the temptation of making an additional note here. Earlier, he said, that medical schools have some responsibility for the training of nurses, health educators, and occupational therapists, and in preceding papers, we heard some of the obligations of medical schools concerning continuation of medical education. I want to place before you the idea, regardless of our idealism and what we would like to do, that soon we shall be doing everything except educating the undergraduate medical student; that our program will be so wide and expansive that we shall not have time to do our primary job.

Those deans who have been away from home will find when they return, a questionnaire from the Association of Medical Colleges: how many more students can you take in the next year and how much will it cost? In any evaluation of a two-year or a four-year school, those who are going to be responsible for it eventually, the private board of trustees or state legislature should be made completely aware of the realistic figures of the cost, both the capital costs and the continuing cost of medical education. Let us assume that Washington University would take an additional twenty students for the freshman class to continue through the four years. If we assume at the present time, that we have in hallways and class rooms and laboratories and libraries and what not, seven hundred square feet of space for each freshman and sophomore student and seven beds for each junior and senior student, the capital cost of an additional twenty students is about four million five hundred thousand dollars, taking hospital beds at only fifteen thousands dollars a bed and construction costs of laboratories at twenty dollars a square foot. Both are very conservative figures. If we assume we lose at least fifteen hundred dollars a year on every ward bed and assume that we can only charge certain tuition rates, which we now charge, the increased cost for twenty students is four hundred thousand dollars a year in maintenance costs.

Let us not lower the quality of medical education in the United States by misleading the legislature and the private boards of trustees that we can take an additional twenty students without running into millions of dollars.

Dr. Stubbs (closing).—Dr. Moore said nothing that I disagree with upon the question of responsibilities being thrown upon medical schools. In some instances, they are already overstrained.

RADIOACTIVE IODINE THERAPY OF HYPERTHYROIDISM: DETERMINATION OF OPTIMUM DOSAGE*

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This study was undertaken with two aims: first, to evaluate radioactive iodine therapy in hyperthyroidism, and second, to explore means of selecting the optimum dose to be administered to each patient.

The iodine used was the carrier-free isotope designated I^{131} produced originally by the neutron bombardment of tellurium in the chain-reacting pile at Oak Ridge, Tennessee, but now prepared free of tellurium from the products of uranium fission at that laboratory. It has a half-life of 8 days, releasing beta and gamma radiations; its decay product is the stable element xenon. Its effectiveness lies in the fact that the thyroid, and particularly the hyperactive thyroid, concentrates the administered radioactive iodine just as it would ordinary iodine, and the short range beta radiations do their destructive work almost entirely within the thyroid and spare the surrounding tissues. To our knowledge no cases of injury of laryngeal nerves or tetany due to destruction of the parathyroid glands have been reported.

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SELECTION OF CASES

From May, 1947 to December, 1950, we have treated 300 thyrotoxic patients with radioactive iodine. These patients were of ward and private status, inpatients and outpatients and all were examined by one or more members of a screening board to determine their fitness for such therapy. This was established by confirming the diagnosis of hyperthyroidism, by attempting to eliminate those patients whose course would be difficult to evaluate, and by favoring those who seemed likely to remain available for follow-up studies.

Radioactive iodine therapy was advised regularly in patients with hyperthyroidism associated with diffuse goiter over the age of 30, and in patients with postoperative recurrence of hyperthyroidism at any age. Certain patients with hyperthyroidism and multinodular goiter were treated with I^{131}. We have felt justified in treating these selected patients because of the data collected by Crile[1] showing that carcinoma was a very infrequent finding in nodular goiters associated with hyperthyroidism. Patients with large nodular goiters were not treated unless surgery had been refused or was contraindicated because of severe complicating disease.

Patients younger than 30 years were not treated without special indications, since their life expectancy would include the long latent period postulated for the development of radiation neoplasm. Werner, Quimby and Schmidt,[2] however, have not found evidence of malignancy fifteen to twenty years after external radiation of hyperactive thyroid glands, and they quote Evans that postradiation malignancy is usually associated with chronic low intensity exposure and not with the brief intense radiation such as is emitted by I^{131} in its decay. An occasional young patient presenting a combination of hyperthyroidism and increased operative risk has been treated. In this group were patients with recurrent hyperthyroidism, patients who have had sensitivity to or failure to respond to antithyroid drugs, and certain patients with serious complicating conditions.

No pregnant woman with hyperthyroidism was treated because of possible danger to the fetus. Patients with colloid goiter and nodular goiter without hyperthyroidism were not treated.

The group consisted of 228 females and 72 males. About four-fifths were between the ages of thirty and seventy; six were younger than twenty years. *Table 1* indicates the age and sex distribution of those treated.

The patients were numbered as they were treated, and those beyond number 155 are either still under the effects of radiation, or have not arrived at a static thyroid state; therefore, evaluation of therapy in their cases is not complete. We shall discuss only patients 1 through 155 who have been followed from 15 months to 44 months. Thirteen of the 155 will not be considered because of the presence of complicating factors which rendered evaluation of therapy unreliable. These factors included death before evaluation or completion of therapy in 6 cases, congestive circulatory failure after apparent control of thyrotoxicosis (2), neurosis (1), carcinoma of the lung (1), and 3 patients who were operated upon because their response was not deemed rapid enough. The remaining 142 will be discussed in detail.

AGE AND SEX DISTRIBUTION OF PATIENTS TREATED

Age Decade	Number of Patients Males	Females	Total
0-10	0	1	1
10-20	2	5	7
20-30	2	24	26
30-40	12	32	44
40-50	22	53	75
50-60	22	57	79
60-70	9	41	50
70-80	3	15	18
			300

Table 1

PLAN OF THERAPY

Radio-iodine was administered routinely in a single treatment room of the Department of Radiology. This precaution was taken in an attempt to avoid widespread contamination of the hospital. Carrier-free I^{131} was standardized against a uranium oxide standard which has closely matched a standard of the Bureau of Standards, and which matches the present (April, 1950) Oak Ridge standard* with an error of about 5 per cent. The dose was administered orally in about 50 cc. of water in disposable paper cups and was given usually on the day of standardization.

In those cases in which the urinary excretion was of interest the patient was provided with

*The Oak Ridge standard has varied considerably in the past two years, and only in recent months has it matched the so-called New York millicurie. The authors wish to acknowledge the assistance of Dr. Martin Kamen of the Mallinckrodt Institute of Radiology, in standardization of the radioactive iodine.

labeled bottles for collection. The bottles were delivered to a central laboratory and handled as radioactive. When excretion studies were not performed, the patient was allowed to use the home or hospital lavatory. No dietary or fluid restrictions were placed on the patients after I^{131} administration.

Dosage in the patients with diffuse goiter was based on the estimation of thyroid size with an attempt to produce a satisfactory remission with a single dose. The patients with nodular goiter and with recurrent hyperthyroidism after previous surgical or external radiation therapy were usually treated with a slightly larger dose of I^{131} than calculated on the basis of estimated thyroid weight. The increment was usually about 1 millicurie and was given because gradually accumulated experience indicated that these patients were more resistant to I^{131}. The estimation of thyroid weight in easily palpable glands of less than 100 grams has been shown to be reasonably satisfactory when performed by an experienced observer.[3] The accurate estimation of the weight of large glands and of glands with substernal projection is impossible. Most of the patients were given 0.2 millicurie per estimated gram of thyroid tissue, but the dosage varied in some cases from 0.08 to 0.6 millicurie per gram, with total single doses ranging from 4 to 50 millicuries.

I^{131} was not given to patients until at least one month after cessation of iodine therapy, cholecystograms, pyelograms, or other iodine intake. Those patients who had been receiving thiouracil derivatives stopped taking the drug at least two days prior to radioactive iodine therapy. Some patients in whom early control of hypermetabolism was critical, were retreated with propyl thiouracil five to seven days after I^{131} administration.

Following treatment the patients were seen with few exceptions after three, six and ten weeks. Patients with more severe hyperthyroidism were seen more often. A second dose of I^{131} was considered necessary if the patient was not euthyroid, or rapidly approaching that state, at the tenth week visit. The size of the second and subsequent doses was based somewhat on the estimated weight of the thyroid, on the degree of clinical response and the change in size of the gland produced by the previous dose. The average second dose was 7 millicuries for patients with diffuse goiter, 8 millicuries for those with nodular goiter, and 6½ millicuries for postoperative recurrent goiter.

RESULTS OF THERAPY

Hyperthyroidism with Diffuse Goiter.—Eighty-three of the 140 patients fell in this group, and of these, 55 had satisfactory remissions produced by one dose of I^{131}. Twenty-three developed some degree of hypothyroidism requiring supplemental thyroid therapy, and 24 were not controlled and were given a second dose. Four patients did not return for follow-up observations.

Fourteen of the 24 patients who received a second dose of I^{131} responded satisfactorily and 4 of these now require thyroid therapy. Five failed to respond and received a third dose; two did not return and three remain under observation.

No remissions were produced by the third dose in this group. One patient has not returned; one is under observation. Of the three patients receiving a fourth dose, one responded well, one failed to respond and was given a fifth dose, and the third is still under observation. The patient who received the fifth dose has responded well with a complete remission after a total of 55 millicuries (*Table 2*).

Hyperthyroidism with Nodular Goiter.—Twenty-eight patients in this group were treated and 13 responded well to a single dose of I^{131}. Six of these now require supplemental thyroid therapy. Thirteen received a second dose, four required a third dose, and one required a fourth dose for remission (*Table 3*).

RESULTS OF I^{131} TREATMENT OF 83 PATIENTS WITH DIFFUSE GOITER

	First Dose	Second Dose	Third Dose	Fourth or Fifth Doses	All Doses
Total treated	83	24	5	3	83
Controlled	55	14	1	2	72
Hypothyroid	(23)	(4)	(0)	(0)	(27)
Not controlled	24	5	3	0	—
Follow-up incomplete	4	5	1	1	11

Table 2

RESULTS OF I^{131} TREATMENT OF 28 PATIENTS WITH MULTINODULAR GOITER

	First Dose	Second Dose	Third Dose	Fourth or Fifth Doses	All Doses
Total treated	28	13	4	1	28
Controlled	13	7	3	1	24
Hypothyroid	(7)	(0)	(0)	(0)	(7)
Not controlled	13	4	1	0	—
Follow-up incomplete	2	2	0	0	4

Table 3

Hyperthyroidism with Postoperative Recurrent Goiter. — Twenty-six patients with recurrent goiter were treated and 19 responded well to a single dose of I^{131}. One of these patients now requires thyroid and one is lost. A second dose of I^{131} was administered to five patients and a third dose to one. One of the five is now euthyroid, one is lost, three are under observation (*Table 4*).

Hyperthyroidism with Post X-radiation Recurrent Goiter.—Five patients had received one to four courses of external radiation as initial treatment for hyperthyroidism, and had recurrences of their disease after an initial favorable response. When given radioactive iodine, one responded to one dose, one to four doses, two patients are under observation after one or two doses, and one is lost (*Table 5*).

COMPLICATIONS OF THERAPY

Hypothyroidism. — Hypothyroidism was the commonest complication following radioactive iodine therapy, occurring in about 25 per cent of all patients treated. Desiccated thyroid was given as soon as clinical signs and symptoms of hypothyroidism were recognized. We have withdrawn desiccated thyroid after various periods of treatment in a number of cases for 1 or 2 months, and all but two were again given the hormone because clinical evidence of hypothyroidism returned. One to two months without replacement therapy may be insufficient time to allow the residual thyroid tissue to return to its maximal potential function. If desiccated thyroid were discontinued for three or four months, we believe that a considerable number of our patients might regain euthyroidism. Desiccated thyroid has not been withheld in the hope of the eventual return of endogenous thyroid function because replacement therapy is highly successful, and without exception our patients have not objected to this inconvenience.

It is noteworthy that while one-third to one-quarter of the treated patients with diffuse and nodular goiter developed some degree of hypothyroidism, only one of the postoperative recurrent hyperthyroidism patients developed hypothyroidism.

Exacerbation of Thyrotoxicosis.—Five patients had a temporary increase in the signs and symptoms of thyrotoxicosis during the week following I^{131} administration. In only one patient, however, was this of clinical importance. Additional radioiodine treatment was not attempted and a thyroidectomy was successfully performed. No measures other than rest and sedation were required during this period of exacerbation. In an attempt to prevent such exacerbations Williams[3] has advised the use of 200 to 300 mg. of propyl thiouracil daily for a few weeks before radioiodine therapy, discontinuing it 4 days before radio-iodine administration. Many of our patients with severe hyperthyroidism received preliminary treatment with propyl thiouracil. Significant exacerbations did not occur in any.

Relapse.—After the attainment of euthyroidism, five patients have had a recurrence of their hyperthyroidism. These occurred from two to six months after maximum improvement. In all cases hyperthyroidism was controlled by additional I^{131}.

Nausea and Anorexia.—Five to 7 days after treatment four patients complained of nausea and anorexia. It was of mild degree, and in three cases was associated with a mild transient tenderness of the thyroid.

Hoarseness. — Two patients developed mild hoarseness lasting 3 or 4 days, about 1 week after I^{131} administration. Recovery was complete in all cases.

Exophthalmos.—Exophthalmos appeared to regress as the disease was brought under control. No patients developed malignant exophthalmos after I^{131} treatment. One patient with malignant exophthalmos was given a single small dose of I^{131} without altering the exophthalmos.

RESULTS OF I^{131} TREATMENT OF 24 PATIENTS WITH POSTOPERATIVE RECURRENT GOITER

	First Dose	Second Dose	Third Dose	All Doses
Total treated	26	6	1	26
Controlled	19	1	0	20
Hypothyroid	(1)	(0)	(0)	(1)
Not controlled	6	1	0	—
Follow-up incomplete	1	4	1	6

Table 4

RESULTS OF I^{131} TREATMENT IN 5 CASES OF POST X-RAY RECURRENT GOITER

	First Dose	Second Dose	Third Dose	Fourth or Fifth Doses	All Doses
Total treated	5	3	1	0	5
Controlled	1	0	0	1	2
Hypothyroid	(0)	(0)	(0)	(0)	(0)
Not controlled	3	1	1	0	—
Follow-up incomplete	1	2	0	0	3

Table 5

Goiter.—Thyroid size was reduced to normal in most of the patients with diffuse enlargement. The decrease in size of toxic nodular goiter was less satisfactory.

SPECIAL PROBLEMS

Dosage.—Few investigators are agreed on the amount of radioactive iodine, which, administered as a single dose, will induce a satisfactory remission of hyperthyroidism, without producing an undesirably high incidence of permanent hypothyroidism. Several clinics[3,4] have met this problem by fractionating the calculated amount of I^{131} into several doses.

The time required to produce a return to normal metabolism should be considered. In favorable cases the response to a single dose of I^{131} may require 3 to 5 weeks. When repeated small doses were used, as long as six months have been needed to control the disease. This prolongation of the disability produced by hypermetabolism greatly reduces the attractiveness of radio-iodine treatment.

The uptake of radioactive iodine determined after the administration of a tracer dose has been studied by others as an aid to the calculation of the required therapeutic dose. The measurement of radio-iodine accumulation in the thyroid, the changes in serum radio-iodine fractions and the urinary excretion of the isotope have proved elsewhere of only limited assistance in estimating the size of the therapeutic dose.[5]

Fig. 1 illustrates the response to various amounts of I^{131} per estimated gram of thyroid in hyperthyroidism with diffuse goiter. Doses less than 0.08 millicurie per gram resulted in failure (2 cases), but with increasing dose there was a higher incidence of successful control of hyperthyroidism. There was fairly constant incidence of hypothyroidism of about 20 per cent in the dose range which gave the best therapeutic response (0.09 millicurie per gram to 0.2 millicurie per gram) and this incidence increased markedly when 0.2 millicurie per gram was exceeded (*Fig. 2*). Most of our patients now receive about 0.15 millicurie per gram of thyroid as an initial dose.

Our experience with multinodular goiter has been too limited for us to suggest the size of the optimal dose. There were more failures than successes following a single dose of less than 0.24 millicurie per gram, and with larger amounts the incidence of hypothyroidism increased rapidly.

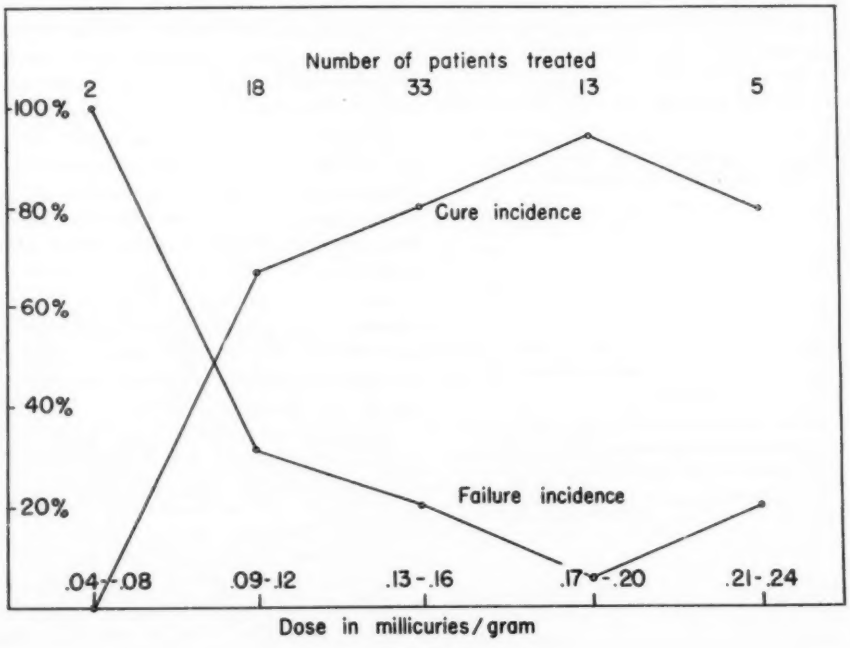

Fig. 1

Diffuse goiter with hyperthyroidism. Response to a single dose of I^{131}.

We have also treated too few cases of postoperative recurrent goiter for analysis since the wide dose range of 0.11 to 0.40 millicurie per gram was administered to only 24 such cases. The results so far seem unpredictable, but the fact that only one case of hypothyroidism developed suggests that we ought to explore the use of higher doses in this group.

The five patients who had received previous external roentgen ray treatment seemed to require larger doses of radioactive iodine. One such patient responded well to 5 millicuries given for an estimated 40 gram thyroid, and another required a total of 43 millicuries in four doses for an estimated 50 gram thyroid. Two are still being observed after multiple doses, and follow-up has not been possible in one patient.

Few generalizations about the refractory cases requiring multiple doses can be made. Ten of our patients required three or more doses of I^{131} containing an average total of 29 millicuries. Five had diffuse goiters, four had nodular goiters, and one had post x-radiation recurrent goiter. Eight of these patients had 48-hour urine excretions examined after a tracer dose of 0.1 millicurie and had an average output of 45 per cent of the administered I^{131} compared to 31 per cent average excretion for 62 patients who responded well to a single dose. Four of these patients had received iodide therapy for a period of months before I^{131} was given but all had discontinued iodine medication at least 30 days before I^{131} was given. Three patients had had recurrent episodes of hyperthyroidism over a period of 2 or 3 years.

Complicating Disease States. — Moderate to severe congestive heart failure was present in 20 patients who were treated with I^{131} for hyperthyroidism. In 11 patients there was definite improvement in the cardiac status with relief of hyperthyroidism. Two patients who had previously required nitroglycerine to control angina no longer needed it after treatment. Five patients with congestive failure have expired in failure, one is lost, one had a thyroidectomy, and two still have severe failure. Two patients who had severe congestive heart failure without hyperthyroidism were treated but no improvement in cardiac function was noted.

Seven patients with diabetes mellitus and hyperthyroidism were treated with I^{131}. They have had remissions of the hyperthyroidism, and the diabetes has become easier to control. A

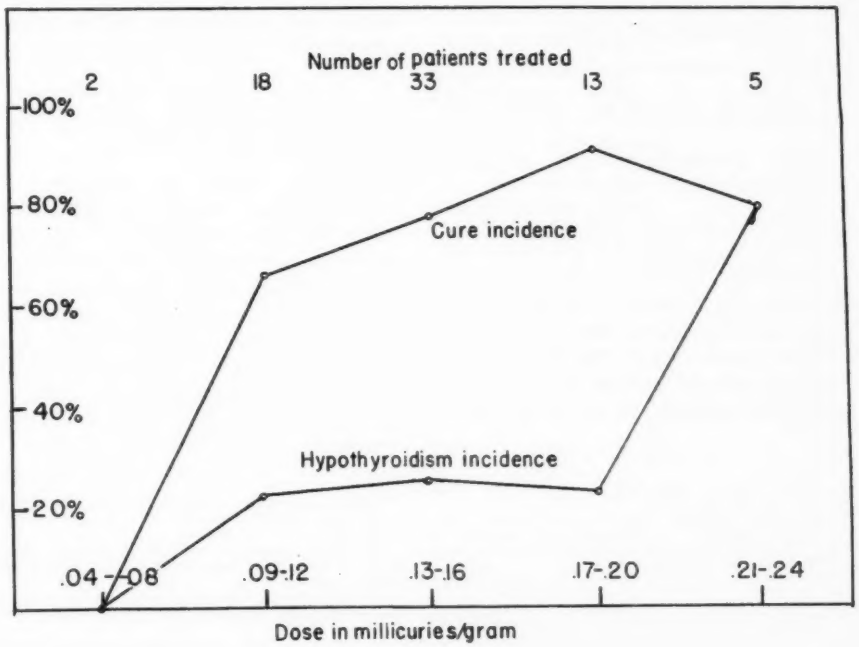

Fig. 2

Diffuse goiter with hyperthyroidism. Comparison of incidence of hypothyroidism to incidence of remission on a single dose of I^{131}.

patient with severe hepatic cirrhosis and hyperthyroidism was treated with I^{131} after an unsuccessful attempt to control the hyperthyroidism with propyl thiouracil. The thyrotoxicosis was controlled with general improvement in the patient's condition.

SUMMARY

We have treated 300 patients with hyperthyroidism with radioactive iodine between May, 1947, and December, 1950. One hundred fifty-five of these who have been followed for six months to three years are discussed.

Patients with hyperthyroidism associated with diffuse goiter, multinodular goiter, postoperative recurrent goiter, and post x-radiation recurrent goiter were treated with a satisfactory remission in 117 patients (76 per cent).

Thirty-five (23 per cent) of these now require some thyroid supplemental therapy.

The effect of different dosages is discussed. Eighty-eight patients (56 per cent) responded satisfactorily to a single dose of I^{131}, averaging 0.2 millicurie per gram of estimated thyroid tissue. An additional 21 per cent responded satisfactorily after two doses. Eleven patients (6 per cent) required three or more doses.

Patients with nodular and postoperative goiters are more resistant to this therapy but will respond if sufficient I^{131} is given.

The diffuse goiters were usually reduced to normal size; the nodular goiters were not.

In general, we feel that radioactive I^{131} is a sound therapeutic measure and a valuable addition to our armamentarium in the treatment of hyperthyroidism in a general hospital possessing adequate technical assistance and physical equipment. With greater clinical experience and the improvement in physical methods a more accurate determination of optimal dose should be possible.

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THE SIGNIFICANCE OF THE RADIOSODIUM SPACE IN HUMAN DISEASE*

A COMPARISON WITH THE THIOCYANATE SPACE

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Clinicians have long recognized the occurrence of edema during the course of such varied and seemingly unrelated disease processes as congestive heart failure, nephritis, chronic malnutrition, cirrhosis, toxemia of pregnancy, myxedema, infectious mononucleosis, serum sickness, trichinosis, pneumonia, and Rocky Mountain spotted fever. The presence of edema is obviously an indication that the distribution of body fluids has been altered. Although various substances have been used in the past to determine the magnitude of the edema, no single substance has been found which is thought to give a true index of the extracellular fluid volume. The purpose of this paper is to discuss briefly the clinical significance of quantitative determinations of the extracellular fluid space, and to present the results of a comparative study of two methods for measuring this space, one employing a positively charged ion, radiosodium, and the other, a negatively charged ion, thiocyanate.

NORMAL ANATOMY

By weight, approximately 70 per cent of the adult human body is composed of water. For example, an average man weighing 155 pounds or 70 kilograms will contain about 49 liters of water. Roughly, two-thirds of this volume, or 34 liters, is intracellular. The remaining 15 liters is extracellular, being distributed between the vascular and interstitial fluid spaces. The interstitial fluid space contains three times as much fluid as the vascular compartment (*Fig. 1*). The composition of the blood plasma differs from that of the interstitial fluid primarily in its greater content of protein (*Fig. 2*).

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*The Na^{24} used was supplied by the National Laboratory, Oak Ridge, Tennessee, on allocation from the U. S. Atomic Energy Commission.

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Some of the characteristics of the internal environment are well known. The sodium ion is the predominant cation in the extracellular fluid, and is normally maintained at a concentration of about 142 milliequivalents per liter. The potassium ion is located principally in cells, only 5 milliequivalents per liter being present in the extracellular fluid. One of the greatest unsolved mysteries in biology today is the mechanism whereby the differential concentration of sodium and potassium is maintained by the tissue cell membrane.

Sodium is such a ubiquitous ion, and the solubility of its salts is so great and their ionization so rapid that, until recently, it was difficult technically to determine its concentration in biologic fluids. By the use of flame spectrophotometry, this obstacle has been largely overcome. It is now possible to measure with relative ease the concentration of sodium and potassium in a solution.

If based on measurements of concentrations alone, however, conclusions as to the nature of the physiologic processes involved may be erroneous. The volume of a space, as well as the concentration of a substance within that space, must be known in order to calculate the total quantity of the substance present, and to determine whether an absolute insufficiency or excess exists.

Methods of Determining the Extracellular Fluid Volume.—In principle, the method of determining the extracellular fluid volume is a simple one. A known quantity of a substance is injected intravenously and its concentration in the blood is measured after sufficient time has elapsed for the substance to reach equilibrium.

Any substance which is employed to measure extracellular fluid volume should meet the following requirements: (1) it must not cross the cell membrane barrier, or must do so very slowly; (2) it must be nontoxic when injected intravenously in the necessary amounts; (3) it must diffuse rapidly in the extracellular fluid space and must quickly attain a state of equilibrium with the native ions; (4) there must be an accurate and simple method for its quantitative measurement.

In the past, the following agents have been used for this purpose: chloride, bromide, thiocyanate, thiosulfate, sucrose, inulin, and mannitol. With the exception of chloride, none of these substances is normally present in the human body. The substance which has been most frequently used in clinical investigation has been the thiocyanate ion. However, it is stated that in certain pathologic conditions the thiocyanate space approaches the calculated total amount of body water;[1] consequently it has not been

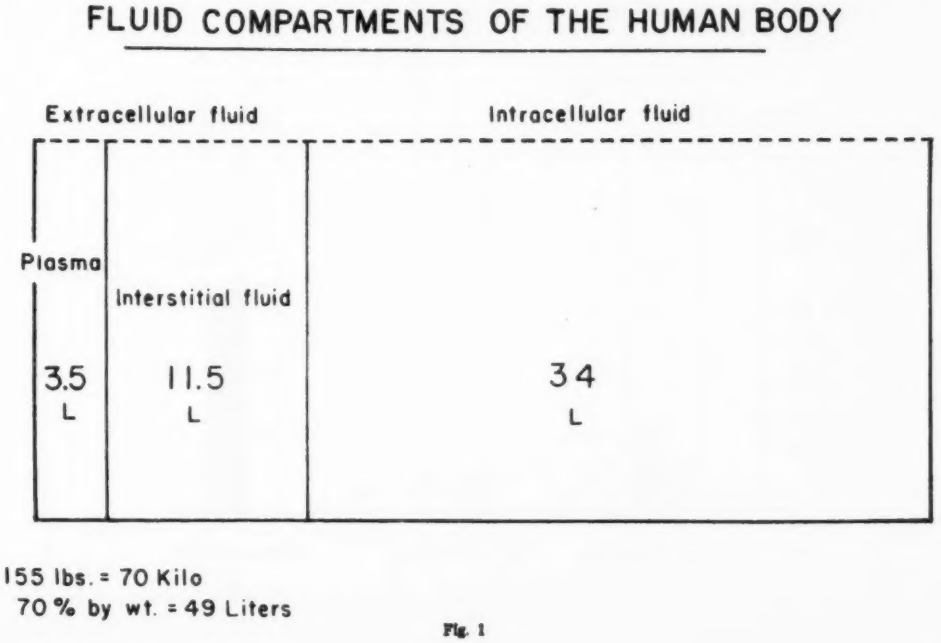

Fig. 1

thought to be a true index of extracellular fluid volume.

Use of Radioactive Sodium.—With the introduction of artificial radioactive isotopes, an invaluable and physiologic substance has been made available for measurement of the extracellular fluid space. Isotopes are atoms of the same atomic number and containing the same number of valence electrons, but differing in atomic mass from ordinary atoms.

One method for producing radioactive sodium is to bombard Na^{23} with neutrons, as is done in the nuclear reactor at Oak Ridge (*Fig. 3*). An additional neutron is crowed into some of the Na^{23} nuclei, and an unstable radioactive isotope (Na^{24}) is thereby formed. Na^{24} changes to a stable state by transmutation into an atom of Mg.[24] In the process a beta ray is emitted and the residual excess nuclear energy is dissipated as gamma rays. The Geiger-Mueller tube is used to measure the ionizations produced by these radiations and to determine thereby the amount of isotope present in a sample.

It should be emphasized that the difference between Na^{23} and Na^{24} is a purely physical one, an extra neutron in the latter. The chemical characteristics of an atom are determined by the orbital electrons; the chemical properties of Na^{23} and Na^{24} are therefore identical. Na^{24} fulfills all the criteria necessary for the measurement of a volume occupied by the ordinary sodium atoms. Since it is chemically indistinguishable from ordinary sodium atoms, its metabolism in the organism will be the same as that of Na^{23} and it will be uniformly diluted among the nonradioactive ions. Another longer lived radioactive isotope, $Na,^{22}$ which is produced in limited quantities in the cyclotron, has been used by Reaser and Burch[5] in investigations on congestive failure.

In measuring the extracellular fluid space with $Na,^{24}$ a tracer amount of a sterile solution of sodium carbonate is given intravenously. After

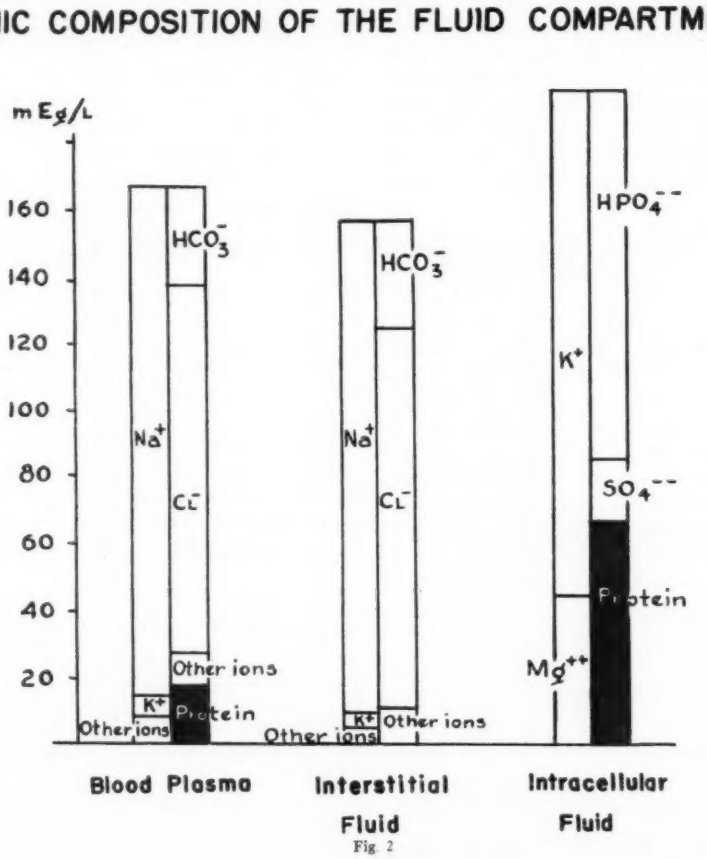

Fig. 2

an interval of 3 hours, a sample of blood serum is drawn and a Geiger-Mueller counter is used to determine its content of the isotope.

There are certain disadvantages and hazards which preclude the routine use of this method in the office or in most hospitals:

(1) Na^{24} decays very rapidly, having a half-life of 14.8 hours. (That is, in a solution containing a certain number of radioactive atoms, one-half of this number would have disintegrated into stable magnesium in 14.8 hours; in the next 14.8 hours, one-half of the remaining quantity would have decayed, and so on.) It is then obvious that geographic proximity to the source of supply and a dependable and rapid method of transport of the isotope to the laboratory are essential.

(2) Na^{24} emits high energy beta and gamma rays; these create potential and unavoidable radiation hazards to the laboratory personnel and to the patient unless proper precautions are used.

(3) The shielding and protective equipment necessary for the safe use of even tracer doses of high energy isotopes is expensive.

The hazards of external radiation to those handling tracer doses of radiosodium are minimal, provided proper technics are employed. The harmful effects of radiation to the patients can be minimized by using the smallest dose necessary to obtain statistically significant counting rates. It has been calculated that the injection of 1.3 microcuries of radioactive Na^{24} per kilogram of body weight delivers a total body radiation of about 0.1 r. over an effective period of about two days, when both the beta and the gamma rays are assumed to be entirely absorbed within the body.[2] The accepted limit of tolerance for continuous irradiation is 0.3 r. per week; hence, from the standpoint of radiation hazard to the patient, it is safe to use tracer doses of 2 to 3 microcuries of radioactive sodium per kilogram of body weight and to repeat them a few times at reasonable intervals (two weeks to two months).

It is then apparent that it would be impractical to use radiosodium in routine determinations, or even for prolonged clinical investigations. However, by making simultaneous determinations of the thiocyanate space and the radiosodium space in normal and abnormal states, and comparing the result, it should be possible to determine whether the thiocyanate method is a valid meas-

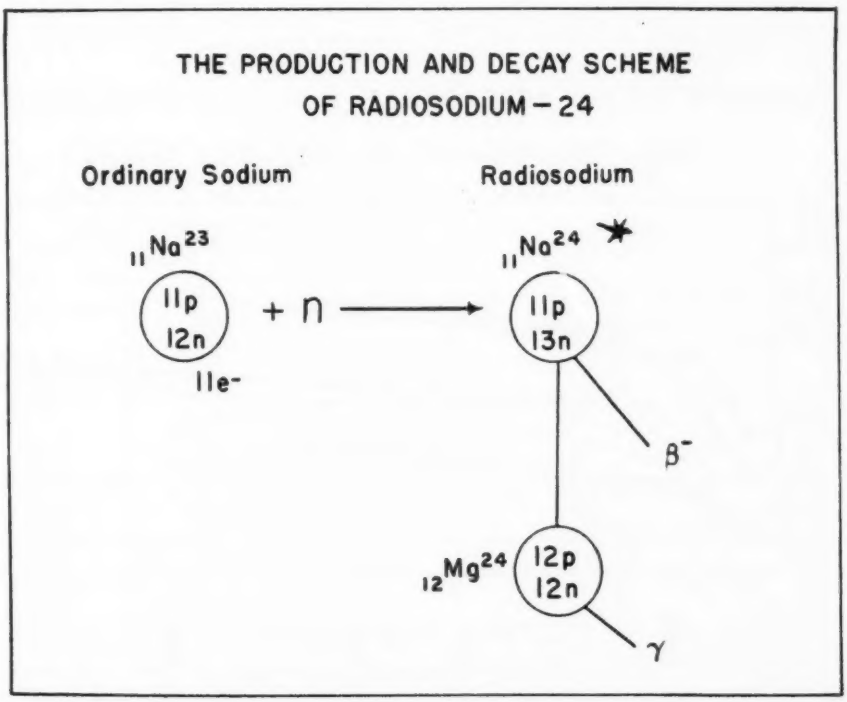

Fig. 3

ure of the distribution of the sodium ion. If so, the technically simpler thiocyanate method can be used for routine determinations of the extracellular fluid space and the isotopic technic reserved for special studies.

COMPARATIVE CLINICAL STUDIES

Simultaneous determinations of the radiosodium and thiocyanate spaces have shown that, following their intravenous injection, Na^{24} and the thiocyanate ion disappear from the blood serum rapidly, and at practically the same rate, up to the third hour (*Fig. 4*). After the third hour, the rate of disappearance of radiosodium from the blood stream is considerably slower than before. Kaltreider, Meneely, Allen and Bale[3] have shown that in normal individuals the comparative values for the thiocyanate and radiosodium spaces are practically identical, when the calculations are based on the three-hour samples. Although it is not established that either the radiosodium or the thiocyanate ion in the extracellular fluid has reached complete equilibrium at three hours, the data show that the two substances measure an identical volume of fluid at that time. The question of whether there is subsequent diffusion of sodium into a larger space after the first three hours is beyond the scope of the present discussion.

It was not known whether the two values would be comparable in individuals in pathologic states. In an effort to clear up this point, we have to date performed a total of 32 simultaneous determinations of the thiocyanate and radiosodium spaces in 20 patients with such varied clinical conditions as hypertension, diabetes, myxedema, toxemia of pregnancy, serum sickness, rheumatoid arthritis, disseminated lupus erythematosus, typhoid fever, arteriovenous fistulas, and exfoliative dermatitis (*Table 1*).

In the three-hour samples the mean thiocyanate space was found to be 17.3 liters; the mean sodium space was 17.4 liters. The mean difference between the simultaneous determinations of the thiocyanate and radiosodium spaces in each

SIMULTANEOUS DETERMINATIONS OF RADIOSODIUM AND THIOCYANATE SPACES IN NORMAL AND DISEASED STATES

	Total Number of Comparative Determinations	Mean Radiosodium Space (Na^{24}) (Liters)	Mean Thiocynate Space (Liters)	Mean Difference	Standard Error
Normal*	9	19.1	19.0	.044	0.16
Diseased states	32	17.4	17.3	.069	1.46

*From Kaltreider, McNeely, Allen, and Bale.

Table 1

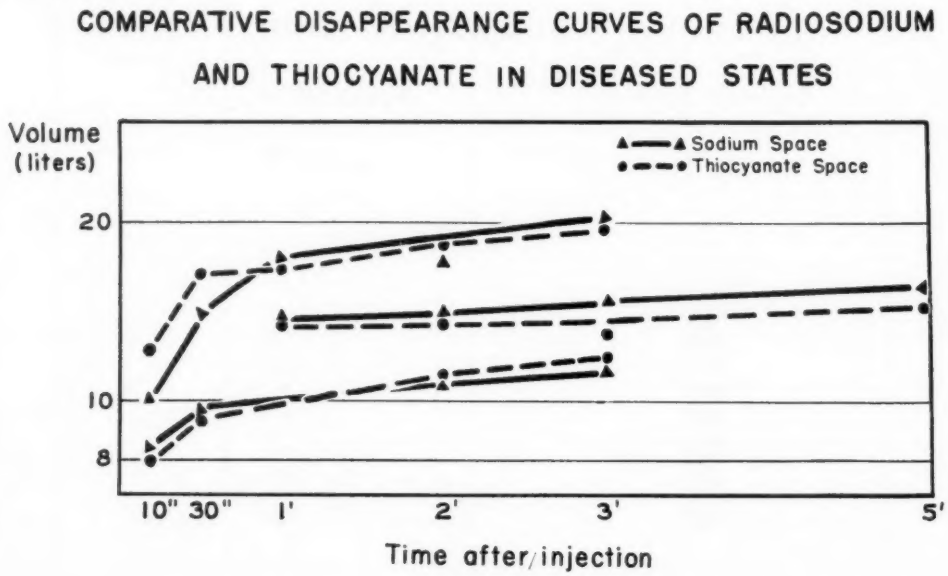

Fig. 4

The figure illustrates the volumes of the sodium and the thiocyanate spaces determined simultaneously from serial serum samples in three representative cases.

individual was 0.069 liter, and the standard error of the difference was 1.46. In normal individuals, the standard error was considerably smaller. It is apparent from these experiments that, although the mean difference between the thiocyanate and the radiosodium space is slight in both normal and abnormal states, there is considerably greater variability in diseased states. The factors which may be responsible for the variability in the different disease processes are being investigated.

It therefore appears, from the available data, that the thiocyanate ion measures a volume of fluid which for practical purposes is comparable to that measured by the radiosodium ion. The radiosodium method is the more physiologic of the two for the measurement of the extracellular fluid space. Because the results obtained by the two methods vary more widely in diseased than in normal states, both methods should probably be employed in critical investigations.

THE VALUE OF STUDIES ON THE DISTRIBUTION OF BODY FLUIDS

The methods now available for studying alterations in the distribution of body fluids may not be directly applicable to practice at present, except in a few instances. Direct measurement of the blood volume may be of value in the therapy of congestive heart failure and in states of circulatory collapse and shock. In patients with the low salt syndrome, determinations of the serum sodium concentration, which is at present estimated indirectly by the serum chloride determinations would be of value. The problem of potassium deficiency in diabetic acidosis and in diarrhea was presented in this Section two years ago by Nicholson and Spaeth.[6]

The fundamental physiologic mechanisms which may be clarified by studies on the distribution of body fluids may have a direct bearing upon the understanding of disease processes and on therapy in the future. To date, no satisfactory method has been devised for measuring directly the volume of the intracellular compartment, the largest pool of water in the body. In all probability, the state of hydration of the cells themselves is of much greater significance than the extracellular fluid volume, or the concentration of ions in it. An indirect method for measuring this volume can be employed[4] by determining

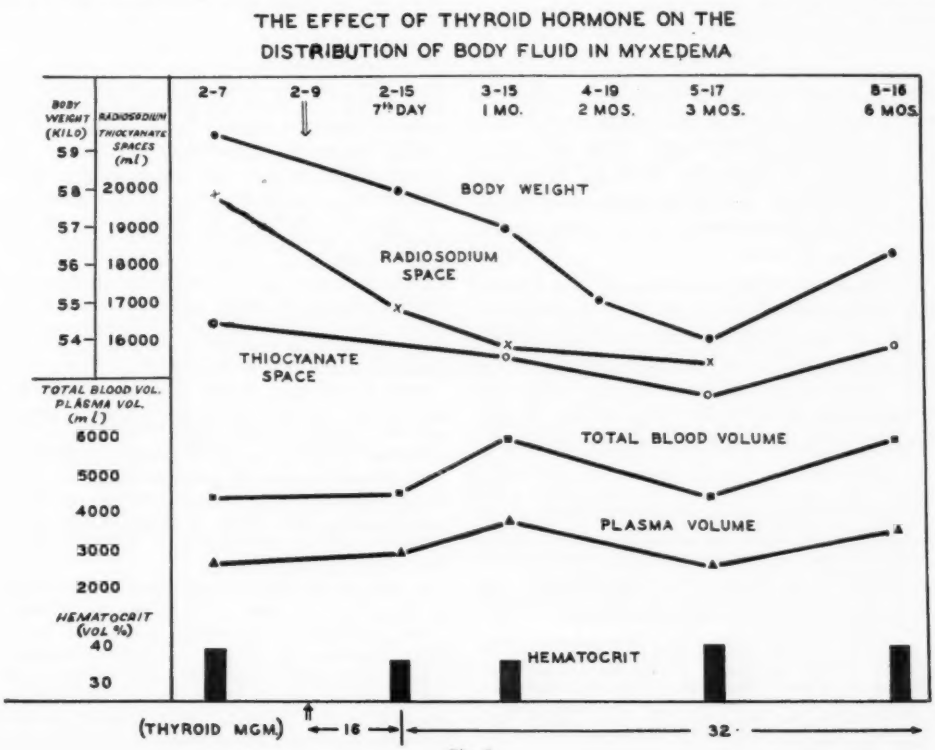

Fig. 5

the difference between the tritium, deuterium and antipyrine space and the volume of the extracellular fluid space.

The following case of myxedema included in our series illustrates the type of information which may be derived from studies on the distribution of body fluids.

In myxedema, the thickening of the skin is thought to be due not to true edema, but to the deposition of a semifluid albuminous substance. Serial determinations of the plasma volume and of the thiocyanate and radiosodium spaces were made during the course of thyroid therapy in a woman with frank untreated myxedema (*Fig. 5*). During the first two months of therapy a progressive decrease in body weight was paralleled by a decline in the radiosodium space. The correlation was so good that it is hard to escape the conclusion that the initial elevation of the radiosodium space was due to edema fluid. The correlation between the changes in weight and thiocyanate space was not so good. As is usually the case in this disease, the total blood volume and the plasma volume were low prior to therapy, and rose to normal levels during the course of treatment.

SUMMARY

Most of the substances which have been used in the past to measure the extracellular fluid space are foreign to the body. Since radioactive sodium, Na^{24} is chemically identical with ordinary sodium, Na^{23} the metabolism and distribution of the two substances in the body should therefore be the same.

Simultaneous determinations of the thiocyanate and radiosodium spaces were performed in individuals with various abnormal physiologic states. Although there was considerable variability in the individual cases, it was found that the mean volume of fluid measured by the two ions in the three-hour samples agreed very closely.

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DISCUSSION (*Abstract*)

Dr. George T. Harrell, Winston-Salem, N. C.—The studies done by Dr. Aikawa employ an isotope dilution technic. By injecting a known amount of the radioactive substance and then determining its concentration in a sample taken after mixing, the total quantity of that particular substance can be estimated. Under certain conditions, where diffusibility of the isotope is free, the distribution and total body content of the material in the body can also be measured. Since the salt is injected intravenously and subsequent measurements are made on samples of blood, the fluid space estimated by the degree of dilution and rate of disappearance from the blood must be extravascular. This space is assumed, on the basis of other investigations, to be predominantly extracellular in the normal individual.

Other isotopes which might be used in an attempt to check the size of the fluid spaces estimated by Dr. Aikawa are the isotopes of potassium, phosphorus and bromine. Chlorine would be a highly desirable isotope to use, since it is freely diffusible and is normally found both within and without cells, but the half-life is so very short that its use is impractical. Alteration in the extracellular (interstitial) fluid space in pathologic processes may also be estimated by measuring the rate of disappearance of various sized protein molecules tagged with radioactive iodine. As the defect in capillary permeability increases with the severity and type of the disease under investigation, larger and larger molecules would be lost from the circulation. A great technical difficulty involved in experiments of this type is the accurate measurement of the small amounts of radiation which can be tolerated by the human body. Further development of the scintillation counter, which is now being shown by a California group in the portion of the scientific exhibit devoted to medicine, gives promise of solving this technical problem.

Dr. Aikawa did not have time to discuss separately each disease process he has studied. The variations noted are apparently not due to differences in individuals; it should be stressed that the alterations seem to be the result of the disease processes. When ordinary chemical technics are used, it has been found that in pneumococcal lobar pneumonia the blood chlorides are low while the blood volume is increased. In Rocky Mountain spotted fever, as has been reported before this Section in the past, the blood chlorides are also low but the blood volume is decreased rather than increased. In congestive heart failure sodium is retained, though it is not yet completely clear whether the total amount of potassium in the body is also increased. In diabetes both sodium and potassium are lost from the tissues. It is of interest that this afternoon in the Section on Pathology a group from Oak Ridge is discussing the effect of irradiation on the permeability of capillary walls and hence on the plasma volume.

In spite of the intensive investigations of this general problem, the knowledge of what goes on within cells is still fragmentary. No technic is available by which direct measurements of the intracellular environment can be made. The radio-autographic technic, when it can be applied, gives a qualitative or semi-quantitative approach to the problem. Exact information on the hydration and ionic concentration of salts within cells

is a very vital matter, since these factors are known to affect the function of enzyme systems on which life itself depends.

The basic studies of research groups such as Dr. Aikawa's are thankless, laborious and often dangerous. Such studies, however, are necessary if we are to obtain basic fundamental scientific knowledge. Only on such a foundation can our ultimate objective be reached, the improvement in therapy of human disease through the understanding of the mechanisms by which illness is produced.

Question.—Did you determine the activity of the edema fluid in the patient with myxedema?

Dr. Aikawa (closing).—In reply to question, we made no attempt to collect edema fluid. This preliminary study was intended to be merely a survey of the comparative values for the radiosodium and thiocyanate spaces in individuals with various pathologic physiologic states. A more comprehensive study is now in progress.

USE OF HYALURONIDASE IN CHRONIC ULCERS*

PRELIMINARY REPORT

By MILTON ENDE, M.D.

Petersburg, Virginia

In 1934 Karl Meyer[1] and Palmer gave the name hyaluronidase to an enzyme which was capable of hydrolyzing hyaluronic acid. This factor has been shown to increase the rate of spread of subcutaneously injected dye and fluids.[2] The chemical basis of the spreading reaction is the depolymerization of hyaluronic acid. This latter substance appears to be the matrix holding connective and epithelial tissue together. Acting by hydrolysis, hyaluronidase reduces the high viscosity of hyaluronate gel thereby facilitating fluid diffusion.

Hyaluronidase has been obtained from spermatozoa, snake venom, many bacteria, carcinoma, lice, spider and bee extract. During inflammation, hyaluronidase is increased in the skin. There has also been shown to exist in blood serum a hyaluronidase inhibitor.[3] This substance increases in a wide variety of systemic diseases.[4]

The principal use of hyaluronidase has been in giving fluids by hypodermoclysis. It has been used in subcutaneous administration of diodrast.[2,5] It brought about the absorption of mucinous plaques in a case of myxedema.[6] In a patient having mesothelioma of pleura and peritoneum it was used to facilitate removal of a fluid of honey-like consistency.

Since one of the causes of chronic ulcers is inadequate nutrition to tissue, it was felt that hyaluronidase might facilitate passage of necessary agents into an ulcerated area thereby promoting healing. Review of the literature fails to reveal this use.

Three patients with chronic leg ulcers have been treated, all showing considerable improvement.

Case 1.—A 25-year-old white male mechanic in early childhood developed an osteomyelitis of his left leg following a skating injury. The patient's leg had subsequently healed but following a slight injury in June, 1950, he developed an ulcer 3 inches by 1¾ inches and approximately ¼ inch in depth. Physical examination was negative. Urinalysis and blood count were normal. The patient was treated for several months with penicillin and local applications. He was then put on bed rest and penicillin was continued for ten days. The ulcer did not appear to heal. Penicillin was stopped and bed rest continued. One ampule of 400 viscosity units of hyaluronidase dissolved in 1 cc. of water was applied to the lesion daily. The patient noted considerable relief of pain in 24 hours. Within one week the ulcer was approximately half its original size and it healed in three weeks.

Case 2.—A 65-year-old white woman was initially seen because of shortness of breath and vomiting. She had suffered from dyspnea, orthopnea, and ankle edema over a period of six months. She had two leg ulcers, one of which had been present for more than 40 years.

Physical examination revealed a dyspneic woman, showing all the signs of heart failure. On her left leg she had a large bandage, of which she would not permit removal. It was not until she had been treated for heart failure with considerable relief that she permitted inspection of the lesions. The ulcer was 5½ by 4½ inches and ½ inch in depth. Muscle tissue was completely exposed in the ulcer. Large varicose veins were present. A smaller ulcer 1 inch by 1½ inches and ⅛ inch in depth was

*Received for publication February 6, 1951.

present on the right leg. Laboratory studies of urine and blood were normal.

The patient was started on hyaluronidase, 400 viscosity units being placed in the wound daily. She was not on bed rest. She noted marked relief of pain. During therapy, the supply of the drug was exhausted for a week and increase in pain was again noted. The ulcer showed gradual formation of granulation tissue. The amount of hyaluronidase was increased to 800 viscosity units but did not appear to bring about any increase in granulation. The smaller ulcer healed in four weeks. The larger ulcer has shown a reduction in size by ½ inch and has granulated to the level of the skin in 2½ months. It is ready for skin grafting.

Case 3.—A 19-year-old colored man has had persistent leg ulcers for eleven months. He has sickle cell anemia. Various agents had been tried in healing the ulcer, including skin grafting and numerous blood transfusions. The ulcer measured 1¼ by 1½ inches and was ¼ inch in depth. A second superficial ulcer 2 inches by 1 was also present. He noted considerable pain relief very promptly after the local application of hyaluronidase. He has not been on bed rest. In six weeks the ulcers had granulated to the skin level.

SUMMARY

Three cases of persistent leg ulcers treated with hyaluronidase have been presented. All showed diminution of pain and rapid formation of granulation tissue. Further investigation of the use of the drug in wound healing is indicated.

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SOUTHERN MEDICAL ASSOCIATION
Forty-Fifth Annual Meeting
Dallas, Texas, November 5-8, 1951

THE DALLAS MEETING OF THE SOUTHERN MEDICAL ASSOCIATION

Arrangements and the program for the Dallas meeting, November 5-8, have been developing for the past six months. A most hospitable letter from the President of the Southern Medical Association, Dr. Curtice Rosser of Dallas, was published in the JOURNAL in June. Dr. Charles L. Martin, President of the Dallas County Medical Society, in this issue reminds physicians of the South again of the friendly warmth which awaits them. Dr. Frank A. Selecman of Dallas is General Chairman of the Committee on Arrangements, and many committees working under him are fast smoothing all details for the forty-fifth annual gathering. Information about hotels will be found on page 665.

Preliminary program plans, which provide for a total of forty-seven half-day sessions, have been completed. The twenty-one sections of the Association will provide a program for every physician, from the general practitioner to the most limited specialist. Each physician will have the needed opportunity to compare his work with that of his peers.

As at all previous meetings, scientific and technical exhibits will present tangible evidence upon new technics and medical and surgical work in general and in particular.

Texas does nothing in a small way. A generation ago when one thought of Texas, one thought of cattle ranches, ten-gallon hats, and six-shooters. Today this state is leading the country in many industrial, educational, fashion, cultural and scientific fields. Outstanding are its three great medical schools and a profession of widely recognized achievement. Texas is a Mecca worthy of pilgrims.

COMPOUND L AND VITAMIN A

In the limelight of clinical progress for the past three years has been cortisone, or compound E. One of a group of steroid substances isolated from the adrenal cortex by Kendall more than fifteen years ago, its clinical activity was discovered only recently. Another product, compound L, was isolated by Reichstein and also by Wintersteiner and Pfiffner[1] in 1936. In structure and in many reactions these substances are closely related to the gonadal hormones. Neither compound E nor compound L sustains life in adrenalectomized animals. Compound L has become available in quantities sufficient for laboratory study. Bodansky and Markardt[2] of Memorial Center in New York City have recently investigated its effects upon the vitamin A content of blood plasma, liver, and kidneys.

Vitamins, like the hormones, are active in such small quantity that there have been few methods of direct measurement of the quantity circulating in the blood or in a given tissue at a particular moment. For many years after the recognition of their importance, they were measurable only by their biological effects, that is, to determine the quantity in a food or other material, laboratory animals on a deficient ration were fed the unknown substance for days or weeks, and the investigator waited to observe whether the animal flourished or sickened. More recently quick

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chemical methods of estimation of a number of them have become available. A dependable chemical reaction for estimation of vitamin A by a colorimetric reaction with antimony trichloride is in use.

It has been shown that testosterone increases the vitamin A level of plasma.[2] Bodansky and Markardt note that if compound L is given young rats on an adequate diet with abundance of vitamin A, the plasma A is considerably reduced, falls to one-half or one-third the normal. At the same time, increased storage occurs in the liver. Liver storage of the vitamin A during shortage is improved if compound L is given. In vitamin A deficiency, the kidney concentration of vitamin A, usually very low, rises. Compound L lowered it. Compound L slightly improved the status of A-deficient rats, diminishing the degree of xerophthalmia.

Vitamin levels in the blood should be important diagnostically, though heretofore the difficulties of their estimation have not permitted their frequent determination. To "do a blood chemistry" in clinical parlance for many years has meant to make a few of the determinations routine in the classic Folin-Wu blood filtrate. Blood sugar, total nitrogen and a few of its partitions, and perhaps the minerals calcium, chloride, and phosphates have been most frequently done. A "blood chemistry" to many practitioners means merely a report of some of the above materials. Determination of vitamin levels in the plasma should be of clinical value and perhaps a useful guide to therapy. The effects of the various hormones upon vitamin levels are physiologically significant. A chemical system is needed for estimation of the level in a small sample of blood of a large number of vitamins and study in large series of cases. It would be valuable in work upon the common nutritional diseases as well as for further understanding of the action of the hormones.

NEW MEDICAL DICTIONARY

The first reference book which a medical student or a practitioner needs is a dictionary, very little medical reading or writing being possible without it. So rapid has been the influx and improvement of drugs in the decade since Pearl Harbor, that a new reference has been severely needed every year, although it has not been available. The twenty-second edition of Dorland's[1] "American Illustrated Medical Dictionary" just off the press four years after the twenty-first would seem very ably and completely to fill a pressing need. First published in 1900, this widely used volume has been revised every two or three years since that time. The period of four years since 1947 is the longest that has elapsed between revisions. The body of medical knowledge to be included in it is so great in this time that its re-examination has been a prodigious task for the scholarly editorial board which has just completed this labor. Omissions have not been found. Its information is completely dependable. Its form is excellent and the 720 illustrations, many in color, are beautiful and valuable. It contains 1,736 pages, is considerably bulkier than the previous edition. In this monumental work the editors have not spared themselves in their scrutiny of every term. This has meant an inhuman amount of reading and study upon numerous subjects in which the literature is vast.

The men who bring out a reference book of this nature have a great responsibility, and almost undue control of the course of medical thought and method, because there is very little competition among dictionaries. The number of textbooks on every medical specialty is legion, but medical dictionaries are very very few. The revision of Dorland has been accomplished under the direction of an able editorial board of three members: Richard M. Hewitt, M.D., of the section on publications of the Mayo Clinic; E. C. L. Miller, M.D., directing Librarian Emeritus of the Medical College of Virginia, and Arthur H. Sanford, M.D., Emeritus Professor of Clinical Pathology, of the Mayo Foundation. Contributors were Lloyd W. Daly, Ph.D., Associate Professor of Classical Studies of the University of Pennsylvania, and Austin Smith, M.D., Editor of the *Journal of the American Medical Association:* a finely chosen and gifted group.

The 1951 edition will have many readers. Some who examine its pages closely will note possibilities for improvement or change. Thirteen pages of appendix are devoted to a listing of new drugs and dosages. A great many proprietary names are here included, and even a number of mixtures. This is a far cry from the advertising principles of George H. Simmons, M.D., the great editor and builder of the *Journal of the American*

1. Dorland, W. A. Newman: The American Illustrated Medical Dictionary, Twenty-Second Edition. Philadelphia: W. B. Saunders Co., 1951.

Medical Association. In its earlier days the American Medical Association constantly fought the use of trade names. A revolution has been taking place in Association-accepted and approved medical advertising in the past quarter-century, a revolution which would be difficult to turn back. It manifests itself tremendously and particularly in the number of proprietary names which appear in the twenty-second edition of Dorland, and which now fill most of the medical literature.

This volume has reached a size which is awkward for frequent use, and it contains numerous words which a medical editor would not encounter in ten years of extensive reading of medical journals. If one contemplates such terms as "hadephobia" (fear of hell), nakuruitis (a form of cobalt deficiency), eleomyenchysis, haasim, gynecotokology, vitaminoscope, vitanition, schweinerothlauf and many others, they seem to complicate the language needlessly, and could to advantage have been omitted.

Seventeen pages are devoted to a listing of acids, which include such names as juglandic acid, humulolamic, ichthulinic, and gynocardic acid. The list would seem to be too few for chemists, and too many for physicians. The volume is said to contain all the terms used in medicine, surgery, dentistry, pharmacy, chemistry, nursing, veterinary science, biology and medical biography. A briefer one, larger than pocket size but for physicians only, would have a wide use. The question of the inclusion of proprietary names in medical literature needs a complete re-examination.

TWENTY-FIVE YEARS AGO

From Journals of 1926

Lunacy Diagnosis.[1]—A report of far reaching importance has just been issued. . . . The commissioners state that there is no clear line of demarcation between mental illness and physical illness. The distinction . . . is in practice no doubt convenient. . . . The key note of the past has been detention; the keynote of the future should be prevention and treatment.

Diploma Mill Chains.[2]—There are well known instances of series of diploma mills being conducted by the same individual or group. Between 1888 and 1892, a series of six diploma mills was chartered in Illinois by one Johann Malok, all of which contained the word, "German" in their titles. . . . The charter of the infamous Oriental University, which had its headquarters at Washington, D. C., was revoked in December, 1923. Immediately thereafter the "business" was transferred to a newly chartered "Cosmopolitan University" located at Poplars, Maryland. . . . Three years ago, two medical schools in Missouri were exposed as being engaged in the sale of medical degrees. . . . To check the sale of fraudulent diplomas requires more drastic action than the revoking of a charter.

Eclampsia Treatment.[3]—The intravenous injection of ten per cent solution of magnesium sulphate is a valuable adjunct in our treatment of the toxemias of pregnancy. It will cause some reduction of blood pressure, reduce edema, increase urinary output, and reduce or control other symptoms . . . it will control the convulsions of eclampsia in practically every case.

Nurses' Names.[4]—It is an accepted fact that a personal relationship between patient and physician, and patient and nurse, is an important factor in aiding the recovery of the patient. . . . In order to add to the personal touch, I have inaugurated at our hospital name badges for nurses. Each nurse has a badge with her name printed on it, which she wears while on duty. . . . The name badges should be worn by all interns, and members of the staff with a designation of the rank, for similar reasons.

1. Foreign Letters. London. Lunacy Reform. J.A.M.A., **87**: 681, 1926.
2. Editorial. Series of Chartered Diploma Mills. J.A.M.A., **87**:594 (Aug. 21) 1926.
3. McNiele, L. G.; and Vruwink, J.: Magnesium Sulphate Intravenously in the Care and Treatment of Pre-eclampsia and Eclampsia. J.A.M.A., **87**:236, 1926.
4. Leff, Marris: Name Badges for Nurses and Staff. Correspondence. J.A.M.A., **87**:264, 1926.

HOTELS FOR DALLAS MEETING

The local Executive Committee for the Dallas meeting has decided that no hotel will be designated as general hotel headquarters. All reservations will clear through the HOUSING BUREAU, Southern Medical Association Meeting, 433 Medical Arts Building, Dallas 1, Texas. In writing to the Bureau, one should give the type and price of accommodations desired, the names of those who will occupy the room or rooms requested, the day and time of arrival, and mode of transportation, whether via train, airlines or private automobile.

The Dallas meeting will be held on Monday, Tuesday, Wednesday and Thursday, November 5-8, the first session beginning at 10:00 a.m. Monday. Here follow the names of the hotels and motels that will furnish accommodations with the local address of each and the rates that will apply:

DALLAS HOTELS

ADOLPHUS, Commerce and Akard Streets	
Single room	$ 4.50-10.00
Double room, double bed	7.00-12.00
Double room, twin beds	8.00-12.00
Double room, double bed with parlor	20.00-22.00
Double room, twin beds with parlor	20.00-22.00
BAKER, Commerce and Akard Streets	
Single room	$ 4.50-10.00
Double room, double bed	6.50-10.50
Double room, twin beds	8.00-13.00
Double room, double bed with parlor	none
Double room, twin beds with parlor	21.00-60.00

See next page for more hotels

CLIFF TOWERS, Zangs and Colorado Streets
- Single room $ 3.00
- Double room, double bed 4.50
- Double room, twin beds 6.00
- Double room, double bed with parlor 10.00
- Double room, twin beds with parlor 12.00

CLIFFTON, 214 West Colorado Street
- Single room $ 2.00- 3.50
- Double room, double bed 3.00- 5.00
- Double room, twin beds 5.00

COTTON BOWL, 600 South Haskell
- Single room $ 3.50- 4.50
- Double room, double bed 4.50- 6.00

DALLAS ATHLETIC CLUB, Athletic Club Building
- Single room $ 4.00
- Double room, double bed 5.00- 6.00
- Double room, twin beds 7.50
- Double room, double bed with parlor 10.00-12.00
- Double room, twin beds with parlor 10.00-12.00

JEFFERSON, 312 South Houston Street
- Single room $ 3.50- 7.00
- Double room, double bed 5.00- 7.00
- Double room, twin beds 6.00-11.00
- Double room, double bed with parlor 20.00
- Double room, twin beds with parlor 20.00

LAKEWOOD, 1818 Abrams Road
- Single room $ 3.50
- Double room, double bed 5.00
- Double room, twin beds 6.00

LAWN, 3718 Lemmon Avenue
- Single room $ 3.50
- Double room, double bed 5.00
- Double room, twin beds 6.00

LAWRENCE, 302 South Houston Street
- Single room $ 3.50- 3.75
- Double room, double bed 5.00- 5.25
- Double room, twin beds 5.75
- Double room, double bed with parlor 9.25

LOMA ALTO, 4518 Lemmon Avenue
- Single room $ 4.00
- Double room, double bed 5.00
- Double room, twin beds 6.00
- Double room, double bed with parlor 8.50
- Double room, twin beds with parlor 9.50

LYNN, 3405 Gaston Avenue
- Single room $ 4.00
- Double room, double bed 5.50
- Double room, twin beds 6.50
- Double room, double bed with parlor 9.50
- Double room, twin beds with parlor 10.50

MAYFAIR, Ross at St. Paul Street
- Single room $ 3.00
- Double room, double bed 3.50
- Double room, twin beds 4.00
- Double room, double bed with parlor 6.00
- Double room, twin beds with parlor 8.00

MELROSE, 3015 Oak Lawn Avenue
- Single room $ 5.00- 8.00
- Double room, double bed 6.00
- Double room, twin beds 7.00- 8.00
- Double room, double bed with parlor 15.00
- Double room, twin beds with parlor 18.00

SOUTHLAND, 102 Murphy Street
- Single room $ 3.50- 6.25
- Double room, double bed 5.25- 6.75
- Double room, twin beds 5.25-12.50
- Double room, double bed with parlor none
- Double room, twin beds with parlor 12.50-16.00

STONELEIGH, 2927 Maple Avenue
- Single room $ 5.00- 6.00
- Double room, double bed 8.00
- Double room, twin beds 8.00- 9.00
- Double room, double bed with parlor 12.00-16.00
- Double room, twin beds with parlor 12.00-20.00

TRAVIS, 1611 Canton Street
- Single room $ 4.50- 5.00
- Double room, double bed 5.50- 7.00
- Double room, twin beds 7.00
- Double room, double bed with parlor 14.00
- Double room, twin beds with parlor 14.00

WHITE-PLAZA, 1933 Main Street
- Double room, double bed $ 4.25- 8.50
- Double room, twin beds 6.00- 8.50
- Double room, double bed with parlor 7.50-15.00
- Double room, twin beds with parlor 12.50-15.00

WHITMORE, 1019 Commerce Street
- Single room $ 3.50- 5.00
- Double room, double bed 5.00- 6.50
- Double room twin beds 7.00
- Double room, double bed with parlor 9.00
- Double room, twin beds with parlor 14.50

DALLAS MOTELS

ALAMO PLAZA, 700 Fort Worth Avenue
- Single room $ 3.50
- Double room, double bed 5.00
- Double room, twin beds 6.00

BELMONT MOTEL HOTEL, 901 Fort Worth Avenue
- Single room $ 5.00
- Double room, double bed 7.00
- Double room twin beds 7.00- 8.00
- Double room, double bed with parlor 20.00
- Double room, twin beds with parlor 22.50

DALLASITE MOTEL, 4126 Central Expressway
- Single room $ 7.00
- Double room, double bed 7.00
- Double room, twin beds 8.00

EL RANCHO-TEL TOURIST COURT, 6131 Hines Boulevard
- Single room none
- Double room, double bed $ 8.00
- Double room, twin beds 9.00

EL SOMBRERO, 7002 Harry Hines Boulevard
- Single room $ 5.00
- Double room, double bed 6.00
- Double room, twin beds 7.00
- Double room, double bed with parlor 12.50

HIGHLAND MOTEL, 6805 Harry Hines Boulevard
- Single room $ 4.00
- Double room, double bed 5.00
- Double room, twin beds 5.50- 6.00
- Double room, double bed with parlor 6.00

LAST FRONTIER MOTEL, 1736 Fort Worth Avenue
- Single room $ 3.50
- Double room, double bed 5.00
- Double room, twin beds 5.00

LA TOURISTA COURTS, 6207 Harry Hines Boulevard
- Single room $ 4.50
- Double room, double bed 4.50
- Double room, twin beds 6.00

SKYLINE, 6833 Harry Hines Boulevard
- Single room $ 6.00
- Double room, double bed 7.00
- Double room, twin beds 8.00
- Double room, double bed with parlor 13.00
- Double room, twin beds with parlor 14.00

MOTOR INN HOTEL OF DALLAS, Fort Worth Cut Off
- Double room, double bed $ 4.00
- Double room, twin beds 5.00

SEVENTY-SEVEN RANCH TOURIST COURT, 2000 Lucas Drive
- Double room, double bed $ 7.00
- Double room, twin beds 8.00
- Double room, double bed with parlor 15.00
- Double room, twin beds with parlor 15.00

TOWER HOTEL COURTS, Hines Boulevard at the Circle
- Single room $ 4.50
- Double room, double bed 6.00
- Double room, twin beds 7.00
- Double room, double bed with parlor 9.00
- Double room, twin beds with parlor 9.00

TOWN HOUSE TOURIST COURTS, 2914 Harry Hines Blvd.
- Single room $ 7.00
- Double room, double bed 7.00
- Double room, twin beds 8.00

Dr. Charles L. Martin

A MESSAGE TO THE SOUTHERN MEDICAL ASSOCIATION FROM THE DALLAS COUNTY MEDICAL SOCIETY

The year 1951 marks the seventy-fifth anniversary of the founding of the Dallas County Medical Society, and it seems most fitting that the celebration of this event be climaxed by our opportunity to play host to the Southern Medical Association. The large medical conventions in America are our post-graduate educational institutions, and have become symbols of our way of life, designed for the free interchange of ideas, the dissemination of all that is new and valuable, and the unrestricted criticism of those things which have not withstood the test of experience.

The medical profession of Dallas is a vigorous, rapidly growing organization, made up of men trained in some sixteen different centers in our nation. Their intensive interest in medical education became evident when they organized the Southwestern Medical College, now a branch of the University of Texas, during World War II, in the face of difficulties which seemed almost insurmountable. For many years they have conducted a superior type of post-graduate instruction, under the auspices of the Dallas Southern Clinical Society, which presents a large conference for more than one thousand physicians each spring, and conducts monthly seminars in the various specialties for smaller groups. Our doctors give freely of their time and energy to insure the success of these educational endeavors, and are proud of the fact that they have never required, or asked for federal aid. This is the group, some eight hundred strong, which issues a warm welcome to the members of the Southern Medical Association, who will visit our city in November.

We hope to mix the friendliness and hospitality, for which Texas is famous, with exhibitions of our scientific achievements in proportions designed to please every registrant who arrives in the Lone Star metropolis, known as big "D".

CHARLES L. MARTIN, M.D.
President, Dallas County Medical Society.

Dallas, Texas, June 10, 1951.

Book Reviews

Methods in Medicine. The Manual of the Medical Service of George Dock, M.D., Sc.D., Formerly Professor of Medicine, Washington University School of Medicine. A Comprehensive Outline for Clinical Investigation, Management, and Treatment of Patients with Various Medical Disorders. By George R. Herrmann, M.D., Ph.D., Professor of Medicine, University of Texas Medical Branch at Galveston. Second Edition, Completely Revised. 488 pages. St. Louis: The C. V. Mosby Company, 1950. Price $7.50.

The second completely revised edition of this manual is one of the best bedside guides available at the present time. Not only will the practitioner appreciate its handiness and abundance of precise, modern information, but also the intern, resident, and medical student will use it to advantage. It could well serve as an applied reference for laboratory technicians.

Of the five major divisions of content, namely: (1) methods of routine case study, (2) clinical laboratory procedures and tests, (3) methods of clinical investigation, (4) therapeutic methods, and (5) dietetic methods, the third is outstanding. This section contains in detailed accuracy all of the recognized standard procedures for special diagnostic work-ups, as in the infectious diseases, metabolic disorders, nutritional diseases, heart disease, and so on.

Seldom is so much of value seen in so condensed a space.

Physical Diagnosis. By Ralph H. Major, M.D., Professor of Medicine in the University of Kansas. Fourth Edition. 446 pages, with 469 illustrations. Philadelphia and London: W. B. Saunders Company, 1951. Price $6.50.

The fourth edition of this book incorporates many improvements in text, illustrations, and format. It continues to be one of the most instructive of the numerous texts on physical diagnosis. Classical descriptions as well as the recent scientific explanations of abnormal findings are presented. The high quality of the illustrations has continued. This text will be of inestimable value to the medical student and the practicing physician.

Conference on Metabolic Aspects of Convalescence. Transactions of the Fifteenth Meeting, New York, March 31-April 1, 1947. Edited by Edward C. Reifenstein, Jr., M.D. Sloan-Kettering Institute, New York. 163 pages, illustrated. New York: Josiah Macy, Jr. Foundation, 1948. Price $2.25.

This pamphlet contains the presentations of speakers and discussions at the Macy Conference as noted in the title.

The contents are divided into two parts. The first is a symposium on isotopes. General discussions are recorded of the use of heavy and radioactive isotopes as tracers in biochemical problems. The second part of the program consists of reports of experiments in progress by various groups concerned with the metabolic aspects of convalescence.

Since the first part is rather sketchy and the last part contains only preliminary reports, there is little of lasting value in this volume.

Conference on Metabolic Aspects of Convalescence. Transactions of the Sixteenth Meeting, New York, October 27-28, 1947. Edited by Edward C. Riefenstein, Jr., M.D., New York. 168 pages. New York: Josiah Macy, Jr. Foundation, 1949. Price $3.00.

Further progress reports on research related to the general subject of convalescence are presented with discussions. The metabolic activities of various steroids are chiefly considered.

Conference on Metabolic Aspects of Convalescence. Transactions of the Seventeenth Meeting, New York, March 29-30, 1948. Edited by Edward C. Reifenstein, Jr., M.D., New York. 246 pages. New York: Josiah Macy, Jr. Foundation, 1949. Price $4.00.

Like the previous conferences on the Metabolic Aspects of Convalescence, this contains reports on current research related to the subject. The adrenal cortex and ACTH receive a large share of the interest.

Metabolic Interrelations. Edited by Edward C. Reifenstein, Jr., M.D., Sloan-Kettering Institute, New York, New York. Transactions of the First Conference, New York, February 7-8, 1949. 193 pages. New York: Josiah Macy, Jr. Foundation, 1949. Price $2.95.

A collection of nineteen articles in the form of preliminary reports of research in various aspects of metabolism. The studies include cartilage, bone, gastric mucosa, intermediary metabolism, ACTH, and steroids.

Metabolic Interrelations. Transactions of the Second Conference, New York, New York, January 9-10, 1950. Edited by Edward C. Reifenstein, Jr., M.D., Sloan-Kettering Institute, New York, New York. 279 pages, with illustrations. New York: Josiah Macy, Jr. Foundation, 1950. Price $3.95.

Following a discussion of the chemistry of the bone salt and the dynamics of calcification, the local factor in bone formation is considered at length.

Color Atlas of Pathology. Prepared under the auspices of the U. S. Naval Medical School of the National Naval Medical Center, Bethesda, Maryland. 546 pages, illustrated with 1053 figures in color on 365 plates. Philadelphia and London: J. B. Lippincott Company, 1950. Price $20.00.

This atlas is a noteworthy contribution to medical literature. The first move toward its creation was made in 1944, at the U. S. Naval Medical School, and the text and reproductions of gross and microscopic specimens

have been prepared by Dr. Charles F. Geschickter, with the collaboration of a large staff of pathologists and technicians. The following organ systems are covered: hematopoietic system; reticulo-endothelial system; respiratory tract; cardiovascular system; liver; alimentary tract; kidney and urinary tract; musculoskeletal system. Each section consists of a descriptive survey and a color unit. The former contains brief discussions of the pathology of principal disease entities, with some remarks on symptomatology, etiology, and therapy. The color units consist of color photographs and photomicrographs of gross specimens and stained sections. These are accompanied by descriptions and brief case histories. Wherever indicated, x-rays and colored drawings have also been added. The color reproductions have been prepared with the greatest care and are altogether admirable.

A second volume, comprising the remaining fields of pathology such as the nervous system, skin, genital organs, and endocrine glands, would certainly be welcomed by many. This atlas provides a post-graduate course in pathology, and to a certain extent in clinical medicine as well. Its many contributors may well be proud of this achievement.

Oral Pathology. A histological, roentgenological, and clinical study of the diseases of the teeth, jaws, and mouth. By Kurt H. Thoma, D. M.D., F.D.S., R.C.S. (Eng.), F.D.S., R.C.S., h.c. (Edin.), Professor of Oral Surgery, Emeritus, and Brackett Professor of Oral Pathology, Harvard University. Third Edition. 1,952 pages, with 1,660 illustrations, 78 in color. St. Louis: The C. V. Mosby Company, 1950. Price $17.50.

In his third revision of Oral Pathology, Dr. Thoma presents a rather comprehensive review of the clinical, roentgenographic and microscopic features of the various disease processes affecting the oral cavity and associated structures. In examining the text, one is impressed with the completeness with which the author has presented the many and diverse pathologic changes occurring in the teeth, jaws and mouth, and the factors concerned in their etiology, pathogenesis, and treatment. The written presentation is well augmented by the use of clinical illustrations, diagrams and photomicrographs. As a rule, the references at the end of each chapter are fairly complete. In a few instances, for example the chapter on dental caries, the author has failed to refer to certain important contributions in the field of caries research. Perhaps the most severe criticism that can be raised is the lack of critical appraisal of some of the references quoted.

The book serves as an excellent reference text for medical and dental practitioners, and for graduate students in medicine and dentistry. As a basic teaching text for undergraduate students, a less comprehensive and more critical work might be of greater value.

Physiology of the Eye. Clinical Application. By Francis Heed Adler, M.A., M.D., F.A.C.S., William F. Norris and George E. de Schweinitz, Professor of Ophthalmology, School of Medicine, University of Pennsylvania, Philadelphia. 709 pages, with 319 illustrations, two in color. St. Louis: The C. V. Mosby Company, 1950. Price $12.00.

The author's earlier book on this subject twenty years ago was the first text devoted entirely to this subject published in America, and because of its excellence it attracted widespread attention. During the past two decades, research in physiology and biochemistry has been extensive in all medical fields; and in this investigation the eye has enjoyed a prominent place not only for ocular problems but also as a key to many general metabolic puzzles. Dr. Adler and his associates have been leaders in many of the fields of ocular physiologic research. This book is a brilliant evaluation of, commentary on, and summary of, the advance of ocular physiology into a major scientific field of investigation; and at the same time it is replete with practical applications of these newly understood facts.

The greater part of the first ten chapters is concerned with anatomical divisions of the eye and adnexa and such physiologic phenomena as the ocular circulation, accommodation and ocular motility. In the last twelve chapters are discussed the effect of light upon the ocular media, the photochemistry of vision, and electrical phenomena of the eye and other related topics.

An ophthalmologist who does not own and read this book is guilty of being uninterested in the fascinating new ocular discoveries and of not giving his patients the benefit of the latest knowledge.

Diseases of the Tropics. By George Cheever Shattuck, M.D., Professor of Tropical Medicine, Harvard Medical School and Harvard School of Public Health, Emeritus. 803 pages, with illustrations. New York: Appleton-Century-Crofts, Inc., 1951.

Diseases of the Tropics impresses one as an eminently practical text. Identification, epidemiology, and treatment are discussed. Greatest emphasis is placed on the commoner tropical illnesses, but all types are covered adequately. There are numerous excellent photographs, charts, and diagrams. This book will be greatly appreciated by physicians, not only in the tropical areas, but also wherever diseases of a tropical nature are encountered. As a convenient reference, it is one of the most significant texts in the field.

The 1949 Year Book of Drug Therapy. Edited by Harry Beckman, M.D., Director, Department of Pharmacology, Marquette University School of Medicine. 718 pages, illustrated. Chicago: The Year Book Publishers, 1950. Price $4.75.

The latest addition to the *Practical Medicine Year Book* series should be welcomed by all. The large number of publications upon therapy has been a matter of concern, and this book should prove to be a great aid in their evaluation. The publishers are to be congratulated in obtaining as editor, Dr. Harry Beckman, whose interest in and knowledge of the field of therapeutics is well known. The selection of material for review is quite good. If there is any criticism to be offered, it is that some of the reviews are needlessly long and that anesthesiology seems to have been slighted.

Plastic and Reconstructive Surgery. A Manual of Management. By Ferris Smith, M.D., F.A.C.S., Consultant in Plastic Surgery, Blodgett Memorial Hospital, Grand Rapids, Michigan. 895 pages, with 592 figures. Philadelphia and London: W. B. Saunders Company, 1950. Price $15.00.

This book embodies an excellent source of reference for plastic surgeons. The author presents various operative methods in common usage with critical comments regarding them, usually giving his own preference.

The section written on the planning and execution of multiple excisions of large face lesions and replacement with adjacent normal tissue is unsurpassed.

Typical cases are shown representing the commoner problems seen by the plastic surgeon. These are illustrated and their operative repair is indicated by excellent photographs and detailed drawings.

This is one of the best manuals of plastic surgery yet published, but its purpose is not to teach the beginner.

A Primer for Diabetic Patients. An Outline of Treatment for Diabetes with Diet and Insulin including Directions and Charts for the Use of Physicians in Planning Diet Prescriptions. By Russell M. Wilder, M.D., Ph.D., F.A.C.P., Professor and Chief of the Department of Medicine of the Mayo Foundation, University of Minnesota; Senior Consultant in the Division of Medicine, Mayo Clinic. Ninth Edition. 200 pages, with illustrations. Philadelphia and London: W. B. Saunders Company, 1950. Price $2.25.

Based upon the premise that "the diabetic patient should be fully instructed in the management of his disease," this booklet contains all the patient ought to know about the nature and the treatment of his condition. Tests for sugar, the technic of insulin administration, the complications of diabetes, and the necessary dietary regulations are clearly discussed in language which is understandable to the lay person of average intelligence. Particularly useful are the sections dealing with the prevention of gangrene, which contains much practical advice, and on substitutions for foods in the standard diabetic diets. This last chapter lists a wide variety of substitutions with recipes, which tend to ease the difficult task of preparing a diversified and palatable diet.

A few revisions have been made. Several chapters are written specifically for the physician, e. g., that on the treatment of acidosis and a chapter on diet. The physician also may well find it profitable to acquaint himself with the entire contents of this booklet.

Introduction to the Regulation of Blood Pressure and Heart Rate. By Corneille Heymans, M.D., Professor of Pharmacology, University of Ghent, Belgium. 60 pages, with charts and diagrams. Springfield, Illinois: Charles C. Thomas, Publisher, 1950. Price $2.00.

Dr. Corneille Heymans' brief monograph on the homeostatic mechanisms maintaining blood pressure and heart rate summarizes the findings and viewpoint of the distinguished Nobel laureate on the subject to which he has made many brilliant contributions during the past generation. Dr. Heymans' discussion, unfortunately, is largely confined to his experiments on dogs, especially perfusion experiments, and the text is centered largely about neural mechanisms, although hormonal factors are briefly cited. The diagrams and bibliography are noteworthy; the latter covers many continental contributions to the subject which might not be found in American texts. For a broader discussion, however, especially relative to man, the reader should be referred to other sources.

Annual Review of Medicine. Windsor C. Cutting, Editor, Stanford University School of Medicine; Henry W. Newman, Associate Editor, Stanford University School of Medicine. Volume I. 484 pages. Stanford, California: Annual Reviews, Inc., 1950. Price $6.00.

This is one of a series of books "designed to cover systematically the current literature in certain major fields of science." While a number of these reviews have previously been published, mostly in the basic sciences, the present volume is the first in the field of medicine. Subsequent volumes will appear at yearly intervals. "Medicine," in this connection, is not limited to internal medicine; for, surgical diseases of the cardiovascular system, neoplastic diseases, obstetrics, neurology, psychiatry, orthopedic surgery, anesthesia, and radiology are among the subjects considered. Each section has been written by an authority in that field.

It should be noted that the authors give a connected and critical account of the noteworthy advances in medicine during recent years, and not merely a review of a number of important articles. What mainly distinguishes this work from other review books is the fact that a great deal of experimental and theoretical material has been included, and that it is aimed, not at the clinician but at "those engaged in teaching and research, and whose background knowledge of the subject is already well established." For the latter group, this constitutes a comprehensive source book of real importance. The extensive lists of current papers appended to each chapter, and a separate annotated list of general review articles enhance its value for purposes of research.

Laboratory Manual for Pharmacognosy. By Edward P. Claus, Ph.D., Professor of Pharmacognosy, University of Pittsburgh, School of Pharmacy. Second Edition. 111 pages, plus fill-in outline pages. St. Louis: The C. V. Mosby Company, 1950. Price $3.25.

This manual is written with emphasis upon the chemical rather than the histological classification of drugs. Fill-in outlines are provided to include additional drugs at the instructor's discretion. The sheets are perforated so that they may be placed in a standard note book after use. The appendix includes some valuable microtechnics.

The Prostate Gland. By Herbert R. Kenyon, M.D. Associate Clinical Professor, Department of Urology, New York University, Bellevue Medical Center. 194 pages. New York: Random House, 1950. Price $2.95.

The diseases of the prostate gland are considered in simple, nontechnical language. The symptoms, methods

of diagnosis, and various methods of treatment of these diseases are discussed. The author begins with the anatomy of the lower urinary tract and this is illustrated by drawings. The next chapter deals with functional disorders of the prostate gland, which is a subject that is sorely neglected in most textbooks. Infectious diseases of the prostate gland are considered and he emphasizes the importance of continuing treatment until the infection is eradicated although symptoms have disappeared early. The importance of early diagnosis of carcinoma is stressed and the subject of hormone therapy is discussed.

The author is biased in his surgical treatment since he leans toward the suprapubic procedures. He says that frequent irrigations of the catheter are necessary after transurethral resection. This is disputed by many urologists.

This book is excellent for the intelligent layman and the general practitioner.

Biological Antioxidants. Edited by Cosmo G. MacKenzie, Department of Biochemistry, Cornell University Medical College. Transactions of The Third Conference, October 7-8, 1948, New York, New York. 146 pages. New York: Josiah Macy, Jr. Foundation, 1949. Price $2.70.

Ten articles with discussions are presented in this *Macy Conference* report. Following an introduction to the chemistry of antioxidation and the action of antioxidants by Michaelis, a number of examples of antioxidants are discussed. Quinones, hydroquinones, vitamin E, flavonoids, steroids, and lipoxidase are covered.

Medical Psychology. A Basis for Psychiatry and Clinical Psychology. By G. K. Yacorzynski, Ph.D., Associate Professor of Nervous and Mental Diseases, Northwestern University Medical School. 596 pages, with 68 illustrations and 25 tables. New York: The Ronald Press Company, 1951. Price $6.00.

It is refreshing to find an excellent text such as this written from the psychobiological viewpoint rather than from the psychoanalytical, with much being written these days that would make one think that psychology completely outdistanced physiology in the advance of psychiatry. While physiology has lagged in the best it is true, particularly in the field of therapy, it has made its advance too. More now than ever before we are beginning to suspect that a better understanding of basic sciences such as biology and even chemistry, will serve as the key to unlock some of the still closed doors to certain mental disorders. The effect of glutamic acid on personality, as well as recent work done with other chemicals suggests that anoxemia is not the only condition that has a profound effect on cerebral activity.

While psychology and physiology have to advance along parallel lines, a text such as Dr. Yacorzynski's "Medical Psychology" makes the physio-biological approach to psychiatric problems clearer than some of the earlier psychobiological texts. Filled with diagrams, charts, examples and graphs it seems more basically scientific. It presents an extensive accumulation of data which clarify a difficult subject for students as well as practicing psychiatrists.

The Adrenal Gland. By Frank A. Hartman, Ph.D., Research Professor of Physiology, The Ohio State University; and Katharine A. Brownell, Ph.D., Instructor in Physiology, The Ohio State University, Columbus, Ohio. 581 pages, with 72 illustrations Philadelphia: Lea and Febiger, 1949. Price $12.00.

The literature on this subject has grown to such proportion that it would seem to be impossible to cover it adequately in a book of this size. Nevertheless, this is what the authors have attempted to do. As a consequence, the book is largely a collection of remarks, summaries, and conclusions gleaned from the literature, with little critical sifting. Sometimes irrelevant material is simply listed.

However, proper reference to the bibliography is presented for each statement and the organization of the text is such that one can locate material without too much difficulty.

The bibliography is notable in that it covers 123 pages and includes the titles of articles. An adequate index is appended.

Biological Antioxidants. Transactions of the Fourth Conference, December 8-9, 1949, New York, N. Y. Edited by Cosmo G. Mackenzie, Department of Biochemistry, University of Colorado School of Medicine; Associate Editors E. V. Jensen, Departments of Surgery and Chemistry, University of Chicago School of Medicine and Ralph T. Holman, Department of Biochemistry and Nutrition, Agricultural and Mechanical College of Texas. 181 pages, with illustrations. New York, New York: Josiah Macy, Jr. Foundation, 1950. Price $3.25.

These transactions include discussion of ions and free radicals, chain reactions as applied to antioxidants, and the biological application with reference to tocopherols and unsaturated fatty acids.

Books Received

Medicine of the Year 1951. Editorial Direction, John B. Youmans, M.D., Dean, School of Medicine, Vanderbilt University; Internal Medicine: Hugh J. Morgan, M.D., Professor of Medicine, Vanderbilt University; Psychiatry: Franklin G. Ebaugh, M.D., Professor of Psychiatry, University of Colorado; Obstetrics and Gynecology: Frank Whitacre, M.D., Professor of Obstetrics and Gynecology, University of Tennessee; Pediatrics: Mitchel I. Rubin, M.D., Professor of Pediatrics, University of Buffalo; General Surgery: Warren H. Cole, M.D., Professor of Surgery, University of Illinois. 298 pages. Philadelphia: J. B. Lippincott Company, 1951. Price $5.00.

Patterns of Disease. By Frank L. Apperly, M.A., M.D. (Oxford), D.Sc. (Melbourne), F.R.C.P. (London), Professor of Pathology, Medical College of Virginia, Richmond, Virginia. 456 pages with 87 illustrations. Philadelphia: J. B. Lippincott Company, 1951. Price $8.00.

Clinical Laboratory Methods. By W. E. Bray, B.S., M.D., Professor of Clinical Pathology, University of Virginia; Director of Clinical Laboratories, University of Virginia Hospital. Fourth Edition. 614 pages with 137 illustrations. St. Louis: The C. V. Mosby Company, 1951. Price $7.25.

A Textbook of Medicine. Edited by Russell L. Cecil, M.D., Sc.D., Professor of Clinical Medicine Emeritus, Cornell University, New York; and Robert F. Loeb, M.D., Bard Professor of Medicine, Columbia University, New York. Eighth Edition. 1,627 pages

with illustrations. Philadelphia and London: W. B. Saunders Company, 1951. Price $12.00.

Clinical Parasitology. By Charles Franklin Craig, M.D., M.A. (Hon.), Sc.D. (Hon.), F.A.C.S., F.A.C.P., D.S.M., Late Colonel, United States Army, Formerly Director, Army Medical School, and Assistant Commandant, Army Medical Center, Washington, D. C.; and Ernest Carroll Faust, M.A., Ph.D., The William Vincent Professor of Tropical Diseases and Hygiene and Head, Division of Parasitology, Department of Tropical Medicine and Public Health, The Tulane University of Louisiana, New Orleans, Louisiana. With a chapter on "Control of Medically Important Arthropods" by Albert Miller, B.S., M.S., Ph.D., Associate Professor of Parasitology (Medical Entomology) in the Department of Tropical Medicine and Public Health, The Tulane University of Louisiana. Fifth Edition. 1,032 pages, with illustrations, some in color. Philadelphia: Lea and Febiger, 1951. Price $12.00.

The Neuroses—Diagnosis and Management of Functional Disorders and Minor Psychoses. By Walter C. Alvarez, M.D., Professor of Medicine, Emeritus, Mayo Foundation, University of Minnesota. 667 pages. Philadelphia: W. B. Saunders Company, 1951. Price $10.00.

Principles and Practice of Obstetrics. Originally by Joseph B. DeLee, M.D. By J. P. Greenhill, M.D., Attending Obstetrician and Gynecologist, the Michael Reese Hospital. Tenth Edition. 1,020 pages with 1,140 illustrations. Philadelphia and London: W. B. Saunders Company, 1951. Price $12.00.

Immunology. By Noble Pierce Sherwood, Ph.D., M.D., F.A.C.P., Professor of Bacteriology, University of Kansas, and Pathologist to the Lawrence Memorial Hospital, Lawrence, Kansas. Third Edition. 731 pages illustrated. St. Louis: The C. V. Mosby Company, 1951. Price $8.00.

Diabetes Mellitus—Principles and Treatment. By Garfield G. Duncan, M.D., Clinical Professor of Medicine, Jefferson Medical College, Philadelphia. 289 pages with illustrations. Philadelphia: W. B. Saunders Company, 1951. Price $5.75.

Handbook of Pediatric Medical Emergencies. By Adolph G. DeSanctis, M.D., Professor of Pediatrics and Chairman of the Department of Pediatrics, Post-Graduate Medical School, New York University-Bellevue Medical Center; and Charles Varga, M.D., Instructor in Pediatrics, Post-Graduate Medical School, New York University-Bellevue Medical Center, New York City. 284 pages with 51 illustrations. St. Louis: The C. V. Mosby Company, 1951. Price $5.00.

Tuberculosis Among Children and Adults. By J. Arthur Myers, M.D., Ph.D., Physician in Charge, Chest Clinic, Students' Health Service, University of Minnesota, Minneapolis, Minnesota. Third Edition. 894 pages with illustrations. Springfield, Illinois: Charles C. Thomas, Publisher, 1951. $12.50.

Primer on Fractures. Prepared by the Special Exhibit Committee on Fractures in Cooperation with the Committee in Scientific Exhibit of the American Medical Association. Sixth Edition. 109 pages, illustrated. New York: Paul B. Hoeber, Inc., 1951. Price $2.00.

Heart Disease. By Emanuel Goldberger, B.S., M.D., Associate Attending Physician, Montefiore Hospital, New York. 392 pages, 221 illustrations. Philadelphia: Lea & Febiger, 1951. Price $10.00.

A Handbook on Diseases of Children Including Dietetics and the Common Fevers. Bruce Williamson, M.D., (Edin.), F.R.C.P. (Lond.), Physician, Children's Dept., Royal Northern Hosp., (Lond.) Sixth Edition. 440 pages with illustrations. Baltimore: The Williams and Wilkins Company, 1951. Price $4.50.

The Student's Handbook of Surgical Operations. By Sir Frederick Treves, Bart., G.C.V.O., C.B., LL.C., F.R.C.S., revised by Sir Cecil Wakeley, K.B.E., C.B., D.Sc., F.R.C.S., F.R.S.E., F.A.C.S. (Hon.), F.R.A.C.S., Fellow of King's College, London, Senior Surgeon to King's College Hospital. Ninth Edition. 580 pages with 269 illustrations. New York: Paul B. Hoeber, Inc., 1951. Price $5.50.

Surgical Forum, Clinical Congress of the American College of Surgeons, 1950. Surgical Forum Committee: Owen H. Wangensteen, M.D., F.A.C.S.; Warren H. Cole, M.D., F.A.C.S.; Robert E. Groos, M.D., F.A.C.S.; Michael L. Mason, M.D., F.A.C.S.; Carl A. Moyer, M.D., F.A.C.S.; I. S. Ravdin, M.D., F.A.C.S. 665 pages with illustrations. Philadelphia: W. B. Saunders Company, 1951.

Handbook of Nutrition. A Symposium. Prepared under the auspices of the Council on Foods and Nutrition of the American Medical Association. Second Edition. 717 pages with illustrations. Philadelphia: The Blakiston Company, 1951. Price $4.50.

Electroencephalography in Clinical Practice. By Robert S. Schwab, M.D., Director of the Brain Wave Laboratory, Massachusetts General Hospital, and Associate in Neurology, Harvard Medical School. 195 pages with 106 illustrations. Philadelphia: W. B. Saunders Company, 1951. Price $6.50.

Fever Therapy. By H. Worley Kendell, M.D., F.A.C.P., Professor of Physical Medicine and Rehabilitation, University of Illinois Research and Educational Hospitals, Chicago, Illinois. 101 pages with illustrations. Springfield, Illinois: Charles C. Thomas, Publisher, 1951. Price $2.25.

The Kidney: Structure and Function in Health and Disease. By Homer W. Smith, A.B., Sc.D., M.S., Professor of Physiology, New York University College of Medicine. 1,049 pages with illustrations. New York: Oxford University Press, 1951. Price $12.50.

Brain Metabolism and Cerebral Disorders. By Harold E. Himwich, M.D., Chief, Clinical Research Branch, Medical Division, Army Chemical Center, Maryland. 451 pages. Baltimore: The Williams and Wilkins Company, 1951. Price $6.00.

Nasal Sinuses. An Anatomic and Clinical Consideration. By O. E. Van Alyea, M.D., Associate Clinical Professor, Department of Laryngology, Rhinology, and Otology, University of Illinois College of Medicine, Chicago. Second Edition. 327 pages, with illustrations. Baltimore: The Williams and Wilkins Company, 1951. Price $9.00.

Introduction to Surgery. By Virginia Kneeland Frantz, M.D., Associate Professor of Surgery, College of Physicians and Surgeons, Columbia University; and Harold Dortic Harvey, M.D., Assistant Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University. New York. 233 pages. New York: Oxford University Press, 1951. Price $2.75.

Current Therapy 1951. Latest Approved Methods of Treatment for the Practicing Physician. Editor, Howard F. Conn, M.D.; Consulting Editors: M. Edward Davis, Vincent J. Derbes, Garfield G. Duncan, Hugh J. Jewett, William J. Kerr, Perrin H. Long, H. Houston Merritt, Paul A. O'Leary, Walter L. Palmer, Hobart A. Reimann, Cyrus C. Sturgis, Robert H. Williams. 699 pages. Philadelphia and London: W. B. Saunders Company, 1951. Price $10.00.

Southern Medical News

ALABAMA

Ceremonies honoring the late Dr. Roy R. Kracke and a presentation of his portrait to the Medical College of Alabama, Birmingham, were held at the Auditorium of the Jefferson-Hillman Hospital, May 20. Dr. Raymond R. Paty, Atlanta, made the presentation of the portrait, and Dr. Tinsley R. Harrison, acting Dean and Professor of Medicine at the Medical College of Alabama, accepted the portrait for the college.

ARKANSAS

Dr. A. F. Barr, formerly of Cherry Valley, has moved to Forrest City where he has formed an association with Dr. J. M. Roy.

Dr. J. W. Branch, Hope, recently took three weeks of postgraduate study in surgery at Cook County Hospital, Chicago.

Dr. Daniel H. Autry, Little Rock, has been elected a Fellow in the American College of Physicians.

Dr. Fred H. Krock and Dr. Thomas P. Foltz, Fort Smith, have been elected directors of Sparks Memorial Hospital there.

Dr. John T. Herron, Little Rock, has been elected State Health Officer of Arkansas.

New officers of the Arkansas Medical Society were elected at the seventy-fifth annual session held recently in Little Rock. Dr. Charles R. Henry, Little Rock, was elected President; Dr. S. A. Drennen, Stuttgart, was elected President-Elect; Dr. Frank Kumpris, Little Rock, First Vice-President; Dr. John H. Wilson, Magnolia, Second Vice-President; Dr. D. W. Goldstein, Third Vice-President; and Dr. R. B. Robins, Camden, was elected delegate to the American Medical Association.

Dr. R. B. Robins, Camden, has been appointed as a member of an advisory committee of physicians as part of the National Doctors Committee for Improved Medical Services. This organization in planning a campaign "to secure wide economies and more efficiency in the present overlapping and competing system of hospital and medical care operated by the government."

Continued on page 36

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Continued from page 672

DISTRICT OF COLUMBIA

Dr. Oscar B. Hunter, Washington, was elected Vice-President of the American Medical Association at the closing session of the House of Delegates at Atlantic City on Thursday afternoon, June 14, a unanimous choice, no other physician being nominated. The Delegate from the District of Columbia making the nomination, in naming the organizations of which Dr. Hunter had been president, mentioned that he had been "president of the *great* Southern Medical Association." Dr. Hunter was President of the Southern Medical Association in 1949, presiding over the annual meeting that year. He had formerly been a member of the Council, of the Executive Committee of the Council, and Chairman of the Section on Pathology, and is now a member of the Board of Trustees.

Dr. Pearce Bailey, Washington, is a member of the Medical Advisory Board of the newly formed National Multiple Sclerosis Society.

Dr. John B. Ross and Dr. William D. Claudy, Washington, have been appointed to the Committee on Bloodbanks of the District of Columbia. The committee was formerly known as the Medical Advisory Committee to the Washington Regional Blood Center.

The Medical Society of St. Elizabeths Hospital, Washington, held its fourteenth annual meeting recently at Hitchcock Hall. Dr. Bernard A. Cruvant is President of the Society.

Recently elected officers of the Board of Directors of the Diabetes Association of the District of Columbia, Inc., are: Dr. Louis K. Alpert, President; Dr. E. Clarence Rice, First Vice-President; Dr. Joseph Roe, Second Vice-President; and Dr. E. K. Hammond Mish, Secretary-Treasurer.

Dr. Winfred Overhosler, Washington, has been reelected President of the Washington Institute of Mental Hygiene. Dr. Dexter M. Bullard and Mrs. John Proctor were elected Vice-Presidents.

The Metropolitan Washington Tuberculosis Conference was held recently in the Federal Security Building North. Dr. John W. Trenis, Washington, President, presided at the conference.

The Georgetown University School of Medicine, Washington, has been awarded an extension grant of $3,650 from the Public Health Service to carry on research in experimental production of benign and malignant bone tumors. Dr. Charles F. Geschickter directs the work.

Rear Admiral Morton D. Willcutts, Washington, Commanding Officer of the National Naval Medical Center, retired recently after 34 years of continuous Naval service. He was given the permanent rank of Vice Admiral upon retiring.

Five District of Columbia physicians have been named to serve on a technical committee on biological warfare to the District Department of Civil Defense. They are: Dr. John C. Eckhardt, Director of the Bureau of Preventable Diseases, District of Columbia Health Department; Dr. Victor H. Haas, Director of the National Microbiological Institute, United States Public Health Service; Dr. Paul K. Smith, Department of Pharmacology, George Washington University School of Medicine, Washington; Dr. John E. Noble, Director of Laboratories, District of Columbia Health Department; and Dr. Richard S. Green, Sanitary Engineer, United States Public Health Service.

Dr. William P. Argy, Washington, has been appointed Medical Director of the District Society for Crippled Children. He is Associate Professor of Clinical Medicine at Georgetown University Hospital.

Dr. Edward B. Tuohy, Washington, has been elected to the American Board of Anesthesiology.

Dr. Bernard S. Gordon, formerly of Washington, has accepted a position with the Spring Grove State Hospital in Catonville, Maryland.

Dr. W. Palmer Dearing, Acting Surgeon General of the Public Health Service, Washington, announced recently that the nation's death rate from tuberculosis dropped about 9 per cent in 1949. Provisional figures for 1950 also show a decrease in the death rate.

Dr. F. Alexander Wetmore (Ph.D.), Secretary of the Smithsonian Institution, Washington, has been elected home secretary of the National Academy of Sciences for a four-year term beginning July 1.

FLORIDA

Dr. H. Marshall Taylor, Jacksonville, was elected President of the American Laryngological Association at its annual meeting in Atlantic City in May. Dr. Taylor was President of the Southern Medical Association in 1935, a member of the Council of the Southern Medical Association 1924-1929, and Chairman of the Section on Ophthalmology and Otolaryngology of the Southern Medical Association in 1925, presiding over that Section at the Dallas Meeting that year.

Dr. Gerald W. Jones, Orlando, recently completed a postgraduate course at Emory University School of Medicine, Atlanta, Georgia, and has returned to his practice in Orlando.

Continued on page 40

THE NEW YORK POLYCLINIC

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DERMATOLOGY and SYPHILOLOGY

A three year course, beginning October, fulfilling all the requirements of the American Board of Dermatology and Syphilology. Also five-day seminars for specialists, for general practitioners, and in dermatopathology.

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A combined course comprising attendance at clinics and lectures; instruction in examination, diagnosis and treatment; witnessing operations; ward rounds; demonstration of cases: pathology; radiology; anatomy; operative proctology on the cadaver.

OBSTETRICS and GYNECOLOGY

A full-time course. In Obstetrics: lectures; prenatal clinics; witnessing normal and operative deliveries; operative obstetrics (manikin). In Gynecology: lectures; touch clinics; witnessing operations; examination of patients preoperatively; follow-up in wards postoperatively. Obstetrical and gynecological pathology. Anesthesia. Attendance at conferences in obstetrics and gynecology. Operative gynecology on the cadaver.

ANESTHESIA

A three months full-time course covering general and regional anesthesia, with special demonstrations in the clinics and on the cadaver of caudal, spinal, field blocks, etc.; instruction in intravenous anesthesia, oxygen therapy, resuscitation, aspiration bronchoscopy.

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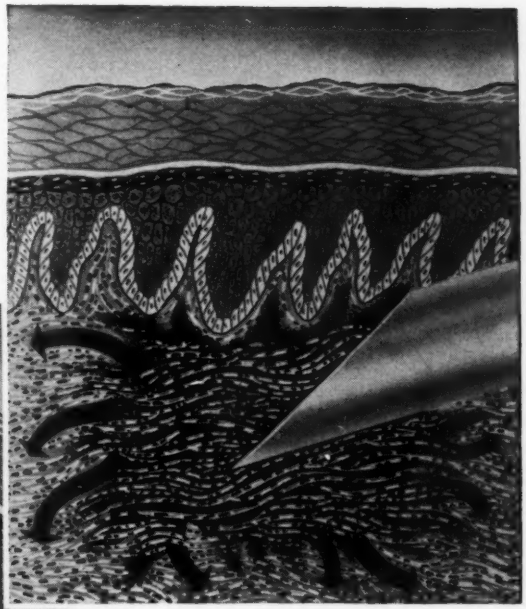

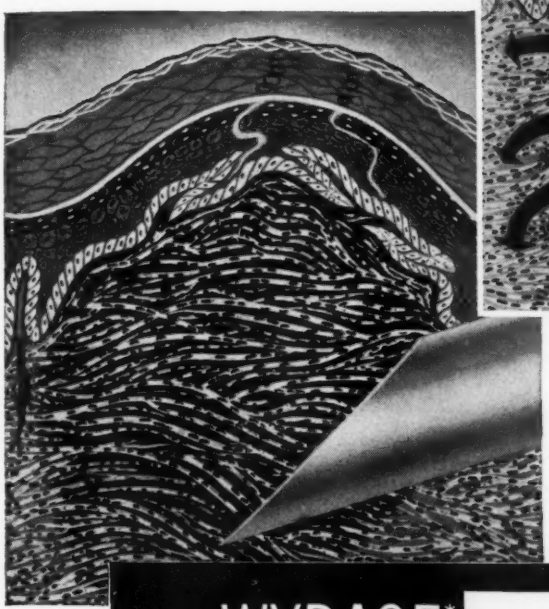

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Highly Purified

For speedy absorption of fluids in hypodermoclysis. Prevents pain from stretching of tissue—nontoxic and apparently nonallergenic.

For More Complete and Widespread Local Anesthesia—fewer injections of local anesthetics required.

WYDASE in dry form is stable indefinitely; keeps in sterile solution for 2 weeks—refrigeration unnecessary.

SUPPLIED: Vials of 150 and 500 turbidity reducing (TR) units.

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Each dose (2 tablets) contains:

'Benzedrine' Sulfate	5 mg.
Acetylsalicylic acid	5 gr.
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Be sure to prescribe *2 tablets per dose*—to get the full benefit of the 'Benzedrine' component.

for the pain, depression, and cramps* of

Edrisal 2 tablets per dose

dysmenorrhea

For unusually severe dysmenorrhea, prescribe 'Edrisal with Codeine'

'Edrisal' and 'Benzedrine' T.M. Reg. U.S. Pat. Off.

1. Janney, J. C.: Medical Gynecology, ed. 2, Philadelphia, W. B. Saunders Company, 1950, p. 365.

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SPERSOL (DOAK)

Tetrachlor-P-Benzoquinone (SPERGON) in carbonwax. Available in 5%, 10% and 20% concentration.

SPERSOL (DOAK) is greaseless, stainless, odorless. Easily removed with water.

Indication: Ringworm of the Scalp
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Suggested Method of Treatment: Hair must be clipped every 10 days. Rub Spersol into the scalp nightly.

In 4 oz., 1 lb. and 5 lb. containers.

Clinical Samples on Request

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Continued from page 36

Dr. Arthur J. Butt, Pensacola, is doing research on the influence of protective urinary colloids in the prevention of renal lithiasis, with the assistance of a research grant from the Wyeth Laboratories, Philadelphia, to the Butt-Douglas Research Foundation.

Dr. M. S. Hernandez, Miami, is at the University of Kansas Medical Center where he is serving a residency in obstetrics and gynecology.

Dr. Cecil M. Jogan, Jacksonville, recently returned to his practice there after attending clinics at Emory University School of Medicine, Atlanta, Georgia.

Dr. George W. Edwards II, Orlando, was recently appointed health officer of the city of Orlando, succeeding the late Dr. Joseph P. Williamson.

Dr. John J. McGuire, Pensacola, has been elected President of the Florida Radiological Society; Dr. Thomas H. Lipscomb, Jacksonville, Vice-President, and Dr. Nelson T. Pearson, Miami, Secretary-Treasurer.

KENTUCKY

Dr. E. L. Pirkey, Louisville, Chairman of the Committee on Scientific Exhibits for the Centennial Meeting of the Kentucky State Medical Association, has announced that applications for exhibits must be completed and submitted before July 15. The meeting will be held in Louisville, October 2-4.

The annual meeting of the Kentucky Surgical Society was held May 19 at French Lick Springs, Indiana, under the leadership of Dr. Pat R. Imes, Louisville, President of the Society.

Charles J. McGaff, Louisville, a sophomore in University of Louisville School of Medicine, has been elected President of the University of Louisville Student American Medical Association.

Dr. H. V. Stewart, Carrollton, has announced that the Tri-County Medical Society, composed of Trimble, Carroll and Gallatin Counties, has become one of the medical societies in Kentucky that are providing emergency call service.

The Committee on Rural Health of the Kentucky State Medical Association met with Agricultural and Public Health leaders recently to discuss methods of improving community health in rural areas. Dr. Walter L. O'Nan, Henderson, is Chairman of the committee.

Dr. C. E. Reddick, Phoenix, Arizona, has returned to Kentucky to take up his new duties as Director of Local Health Services and Deputy Health Commissioner of the State Department of Health.

A Kentucky State Medical Association Dental Committee has been appointed to serve with a similar committee of the Kentucky State Dental Association to consider matters of interest to the two professions. Members of the committee are: Dr. John J. Wolfe, Louisville, Chairman; Dr. Thomas J. Crume, Owensboro; and Dr. Allen L. Cornish, Lexington.

Dr. Joseph R. Griffitt, formerly of Nicholsville, has taken over the practice of Dr. E. N. Rush in Mt. Washington. Dr. Rush has been called into service.

Dr. Irvin H. Sonne, Louisville, retired, has purchased the Methodist Evangelical Hospital which he will operate as an old persons' home.

Dr. W. R. Miner, Covington, has been elected President-Elect of the Southeastern Section of the American Urological Society which met in Memphis, Tennessee, recently.

LOUISIANA

The Louisiana State University School of Medicine, New Orleans, has been awarded a grant by the Mississippi Division of the American Cancer Society. The grant will be used to conduct a series of clinics and seminars for physicians in areas in the southern half of Mississippi.

Dr. George Edward Burch, New Orleans, has been appointed a member of an advisory committee of physicians as part of the National Doctors Committee for Improved Medical Services.

MARYLAND

Dr. Robert V. Seliger, Baltimore, Director of the Neuropsychiatric Institute of Baltimore, has been appointed Medical Consultant to the Canadian National Committee for Education on Alcoholism, Inc., Montreal.

The Woman's Auxiliary of the Baltimore City Medical Society has created a medical scholarship fund designed to aid rural medicine. The fund was set up in honor of Dr. Crawford Long, first successful user of anesthetics.

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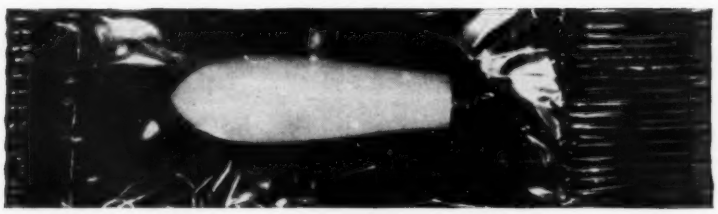

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Convenient: Individually packed. No refrigeration necessary.

Formula: ephedrine hydrochloride 0.22%; benzocaine 5.00%, in a special emulsifying base. Average weight of 1 suppository—1.8 Gm.

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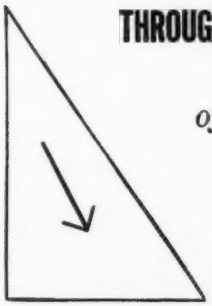

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of the symptoms of urinary tract infection

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An analysis of symptomatic relief in 118 cases treated with Pyridium shows:*

Urinary frequency promptly relieved in 85% of cases.

Pain and burning decreased in 93% of cases.

*Kirwin, T. J., Lowsley, O. S., and Manning, J.: Effects of Pyridium in certain urogenital infections, *Am. J. Surg.* **62**: 330-335, December 1943.

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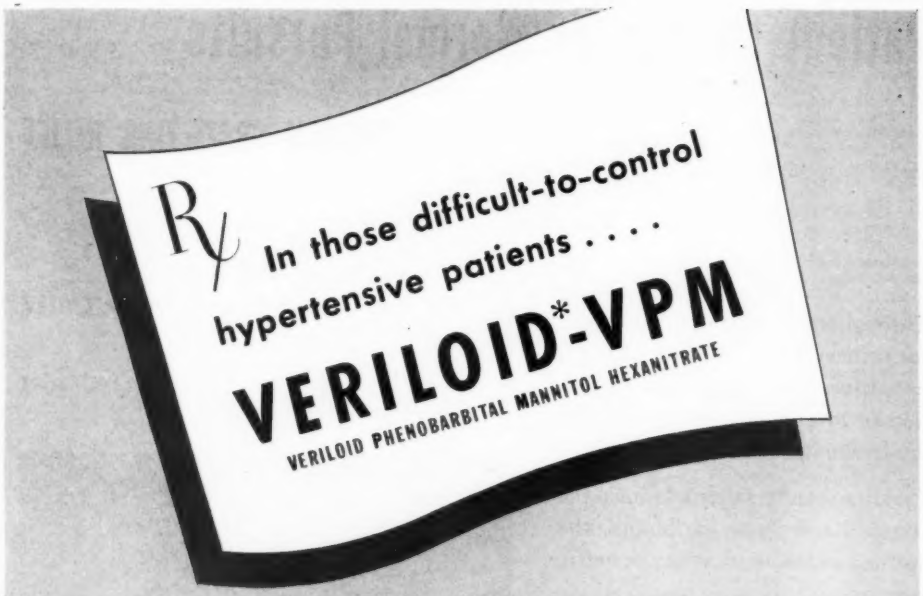

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References...

J. Clin. Endocrin. **9,691 (1949).**

Trans. of Conference on Metabolic Aspect of Convalescence, **17th Meeting, Josiah Macy, Jr. Foundation, New York, Mar. 29-30, 1948.**

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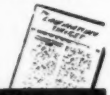
Write for a sample copy of The Gradwohl Laboratory Digest full of helpful hints on improved laboratory technique.



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Dr. Detlev W. Bronk, (Sc.D.), Baltimore, has been elected President of the National Academy of Sciences which met in Washington recently.

MISSISSIPPI

Dr. Lamar Arrington, Meridian, has been elected President-Elect of the Mississippi State Medical Association which met in Biloxi, May 15-17. Dr. Arrington is a member of the Council of the Southern Medical Association representing Mississippi and is Vice-Chairman of the Section on Pediatrics.

MISSOURI

The St. Louis University School of Medicine, St. Louis, has received a trust valued at $33,000, anonymously, which will be known as the Ellen McBride Cancer Research Endowment.

The St. Louis University School of Medicine held its annual Alumni Association dinner in Atlantic City, New Jersey, June 13.

The Washington University School of Medicine, St. Louis, and the Economic Cooperation Administration of the United States have signed a contract for a cooperative teaching program between the school of medicine and the two medical schools of Thailand in Bangkok. Staff members of the school of medicine will establish residence in Bangkok with grants-in-aid for a two-year period, to teach in the two medical schools there. Thailand physicians will go to St. Louis for advanced training and study at the Washington University School of Medicine. The program includes exchange of nurses, medical technicians and nurse anesthetists.

NORTH CAROLINA

Dr. Frank Ray Lock, professor of obstetrics and gynecology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, has been appointed medical director of the North Carolina Baptist Hospital, Winston-Salem, to succeed Dr. C. C.

Continued on page 48

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BREWERS' YEAST

STILL THE DEPENDABLE STAND-BY FOR PELLAGRA

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Outstanding results with Furacin

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IN CHRONIC VARICOSE ULCERS

In a female aged 47 years, varicose ulcers had proven refractory to rest, elevation of the leg, compresses and diverse topical applications. There was profuse discharge with Micrococcus pyogenes aureus, Streptococcus pyogenes, P. aeruginosa (pyocyaneous). *See 1 above.*

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Literature on request

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Medal of Honor

Master Sergeant Travis Watkins, of Gladewater, Texas—Medal of Honor. On September 3, 1950, near Yongsan, Korea, Sergeant Watkins was wounded and paralyzed from the waist down. Ordering his squad to pull out and leave him, he stayed behind and died covering their withdrawal.

Sergeant Watkins gave his life for freedom. What can you do?

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For your Defense Bonds strengthen America. And if you will make our country strong enough now, American boys may never have to give their lives again.

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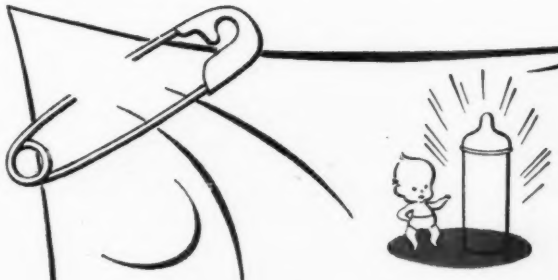

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Lactogen contains all the ingredients of a well-balanced infant formula. In addition, it is fortified with iron to compensate for the deficiency of this mineral in milk.

Easily Prepared . . . Merely Add Water

Lactogen is simple to use. The prescribed amount is stirred into warm, previously boiled water. Either a single feeding can be prepared, or the entire day's quantity can be made up and stored in the refrigerator until used.

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NOTABLY HIGH IN PROTEIN CONTENT
Lactogen contains a generous amount of protein . . . more than enough to satisfy every protein need of the rapidly growing infant.

since 30%
OF HAY FEVER VICTIMS EVENTUALLY DEVELOP ASTHMA...[1,2]
it is important to note that:

"Alleviation of the patient's symptoms with the antihistaminics will not prevent asthma."[2]

Preseasonal treatment, by specific hyposensitization begun six to twelve weeks before the anticipated exposure to tree pollens, grasses, and weeds, affords "excellent relief" in 80 to 85 per cent of cases—with greatly reduced likelihood of complications such as asthma and sinusitis.[2,3]

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DRY POLLEN DIAGNOSTIC SETS

contain at least 23 vials of selected windborne pollens representing the major causative factors in your area, plus a vial of house-dust allergen. Each vial provides enough material for about 30 tests; diluent furnished with each set. Price, $7.50.

POLLEN TREATMENT SETS

provide serial dilutions of single pollens of your choice, or pollen mixtures chosen from our 21 stock mixtures. Each set contains five 3-cc. vials of the following concentrations: 1:10,000; 1:5,000; 1:1,000; 1:500; and 1:100. Dosage schedule accompanies each set. Price, $7.50.

SPECIAL MIXTURE TREATMENT SETS

prepared according to your patient's individual sensitivities. Each set contains five 3-cc. vials in the same dilutions as above. Ten-day processing period required. Price, $10.00.

1. Cooke, R. A.: in Textbook of Medicine (Cecil). Philadelphia, W. B. Saunders Company, 1947; seventh edition, p. 528.
2. Nevius, W. B.: J. M. Soc. New Jersey 46: 17 (1949).
3. Rosen. F. L.: ibid. 45: 389 (1948).

THE ARLINGTON CHEMICAL COMPANY
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Continued from page 44

Carpenter, who will devote full time to duties as dean of the medical school and professor of pathology.

The Bowman Gray School of Medicine of Wake Forest College has announced that 61 students received their M.D. degrees in commencement exercises June 10 and 11. The tenth anniversary of the establishing of the Bowman Gray School was observed at that time.

Dr. C. Hampton Mauzy, Winston-Salem, associate professor of obstetrics and gynecology at the Bowman Gray School of Medicine of Wake Forest College, was elected President-Elect of the North Carolina Obstetrics and Gynecology Society at a recent meeting at Mid-Pines.

Dr. Mary T. Martin Sloop, Crossmore, has been selected American mother of 1951 by the American Mothers Committee of the Golden Rule Foundation, an organization devoted to the welfare of mothers and children. Dr. Sloop founded the Crossmore School for Underprivileged Children and has been credited with greatly improving the general welfare of Avery County. She is the wife of Dr. Eustace Sloop and the mother of two children, also physicians.

Dr. George D. Wilson, Asheville, has been appointed a member of an advisory committee of physicians as part of the National Doctors Committee for Improved Medical Services, an organization which plans a campaign to eliminate waste in government medical care expenditures.

The Duke University School of Medicine, Durham, held its Spring Medical Postgraduate Course in Durham, June 18-21.

OKLAHOMA

Dr. W. J. White, formerly of Hampton, Arkansas, has associated with Dr. Ralph Martin, Sand Springs.

The annual meeting of the Oklahoma State Medical Association was held May 21-23 in Tulsa.

The Oklahoma Rheumatism Society met in Tulsa, May 20, at the Mayo Hotel under the presidency of Dr. Sumner Y. Andelman, Tulsa.

SOUTH CAROLINA

Dr. Robert P. Jeanes, Easley Ophthalmologist, has been released from duty in the armed services and has returned to Easley to take up his practice there.

Dr. W. A. Woodruff, Spartanburg County, has been appointed an Honorary Trustee of the Medical College of South Carolina by Governor Byrnes.

Dr. O. Z. Culler, Orangeburg, has been elected to the board of trustees of the Orangeburg Hospital.

Dr. T. G. Herbert, Charleston, has resumed his association with Dr. Patricia Carter in the practice of obstetrics and gynecology in Charleston. He was recently released from the Navy.

Dr. W. R. Barron, Columbia, has been elected Chief of Staff of the Baptist Hospital.

Dr. R. L. Sanders, Columbia, has been appointed chairman of the Building Fund Committee of the American Academy of General Practice.

The Atomic Energy Commission has awarded the University of South Carolina, Columbia, an unclassified research contract for the study of mechanisms of allylic fluorination under the direction of Dr. H. W. Davis.

TENNESSEE

The Tennessee State Medical Association has announced that 570 physicians and 72 laymen registered at the Annual Meeting held in Nashville recently. It was the largest registration in 17 years.

Dr. Hugh Edward Green, Smith County, and Dr. Johnnie Clariday, Smith County, have purchased the Cloyd Hotel in Red Boiling Springs and plan to convert it into a hospital. The hospital, a 75-bed building, will be opened around July 1, 1952.

Dr. E. White Patton, Chattanooga, has been placed on reserve status by the Navy and has reopened his practice in Chattanooga.

Dr. R. O. Glenn and Dr. Paul J. Bundy, Mountain City, have been named to the initial staff of Johnson City's Memorial Hospital.

Dr. M. M. Young, Kingsport, has received a commission of Senior Assistant Surgeon in the U. S. Public Health Service. He will be stationed in Dallas, Texas.

Dr. John W. Baird recently opened offices in Memphis for the practice of dermatology.

Dr. Daugh W. Smith, Nashville, has been elected President-Elect of the Tennessee State Medical Association, and Dr. R. H.

Continued on page 52

to overcome smooth-muscle spasm . . .

to allay anxiety . . .

to help combat depression . . .

to promote restful sleep

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TRADEMARK

- Provides the recognized sedative action of ***phenobarbital***

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- the antispasmodic effect of ***belladonna alkaloids***

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BELBARB* Tablet #1 per tablet	¼ gr.	hyoscyamine, atropine, and scopolamine in fixed proportion, approximately equivalent to Tr. Belladonna, 8 min.	Bottles of 100, 500, and 1,000 tablets
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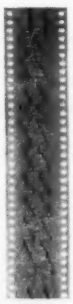
The permanent photographic records made with the AO Ophthalmograph give you a clear picture of the way the two eyes function together. For the Ophthalmograph charts actual binocular performance, providing a further objective measure of the inferences made from routine tests, and helping to check the effectiveness and progress of corrective procedures.

In this exclusive AO instrument film moves through a camera at the constant speed of 2.5 feet per minute. Light reflected from the patient's corneas, produces a graph on the film as the patient moves his eyes in reading. The Ophthalmograph also automatically develops the film within eight minutes.



Graph of normal eye movement.

Graph of high school girl who has difficulty maintaining binocular fusion in reading at near point.

Graph of 37 year old man who is very nearsighted. Never having learned to control his eyes in the return sweep, he feels his way back to the beginning of each new line, causing the "reverse stairways".

Graph of 5th grade boy who has consistently failed and repeated 3 grades, reveals immature reading habits.

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FOR THE FAILING HEART

Theocalcin, theobromine-calcium salicylate, exerts a twofold action: 1) it is an efficient diuretic, and 2) it stimulates the heart muscle.

For most cases of congestive heart failure, a dose of 1 or 2 Theocalcin Tablets given 3 times a day will suffice. Theocalcin is well tolerated and not likely to cause nausea or headache.

Theocalcin Tablets, 7½ grains (0.5 Gm.) each. Powder, for prescription compounding.

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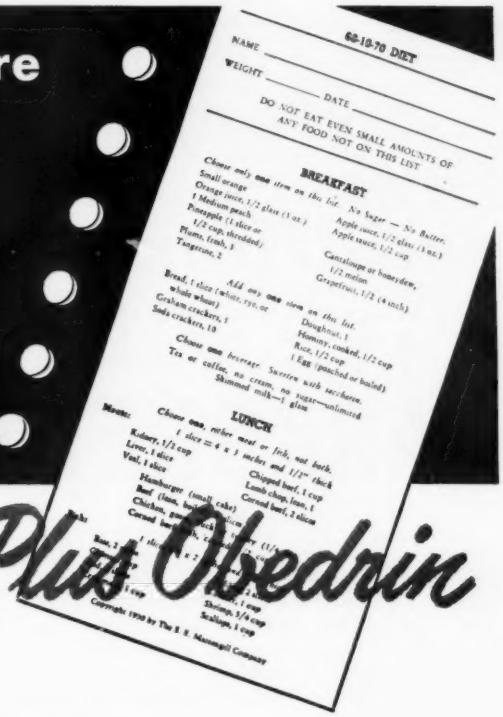

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CURBS THE APPETITE

Through the use of the unique 60–10–70 diet and Obedrin tablets, considerable weight can be lost without troublesome hunger or impairment of nitrogen balance. Patient cooperation is assured because morale is kept high and excessive fatigue due to a nutritionally unsound diet is avoided.

MAINTAINS GOOD NUTRITION

The 60–10–70 diet allows free choice of many foods and supplies 70 Gm. of protein, 60 Gm. of carbohydrate, and 10 Gm. of fat, approximately 610 calories. The diet sheets are complete and self-explanatory, making it easy for the patient to do his share.

Obedrin permits adequate dosage of Semoxydrine Hydrochloride (methamphetamine) to suppress appetite. The corrective dose of pentobarbital cancels excessive central nervous stimulation, while vitamins help maintain the patient's sense of well-being.

FORMULA

Semoxydrine Hydrochloride	5 mg.
Pentobarbital Sodium	20 mg.
Ascorbic Acid	100 mg.
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Obedrin is supplied in bottles of 100, 500, and 1,000 yellow grooved tablets.

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NARKOGEN (Tilden) contains CHLORAL HYDRATE, "still the standard hypnotic of its class," and "one of the most reliable of sedative agents."* Ordinary doses act promptly to produce a natural, physiological sleep which "lasts at least several hours" and the patient "awakens refreshed."*

- **Bromides and Hyoscine Hydrobromide potentiate the hypnotic, calming and spasmolytic effects of the Chloral hydrate in NARKOGEN.**

	per fluid ounce	per 100 cc.
Chloral Hydrate	..80 gr.	17.5 Gm.
Potassium Bromide	..80 gr.	17.5 Gm.
Hyoscine Hydrobromide	..1/25 gr.	9 mg.
Horsenettle, Wild Lettuce and Celery Seed.		
Alcohol 10%.		

USE NARKOGEN for restful sleep in insomnia, for sedation and control of spasms in highly nervous and excitable patients. Supplied in pint and gallon bottles.

Samples and *new literature to physicians on request.

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The Oldest Manufacturing Pharmaceutical House in America

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Continued from page 48

Kampmeier, Nashville, has been elected Secretary-Editor. Dr. Ernest G. Kelly has been installed as President.

A special apparatus for administering rays of radioactive cobalt will be delivered to the Oak Ridge Institute of Nuclear Studies and to the M. D. Anderson Hospital, Houston, Texas. The radio-cobalt program at Oak Ridge is under the direction of Marshall Brucer, Chairman of the Medical Division. The Institute and the M. D. Anderson Hospital, affiliated with the University of Texas, will cooperate in studies and tests on radioactive cobalt and its effects on cancers.

The 1951 Oak Ridge Summer Symposium on "The Role of Engineering in Nuclear Energy Development" will be held August 27 to September 2. Information on the symposium can be obtained from the University Relations Division, Oak Ridge Institute of Nuclear Studies, P.O. Box 117, Oak Ridge, Tennessee.

Dr. Dempsie B. Morrison, associate professor of chemistry of the University of Tennessee Medical Units, Memphis, will be the director of the Section of Clinical Chemistry to be established by the University of Tennessee College of Medicine, it has been announced by Dr. O. W. Wyman, Vice-President of the Medical Units and dean of the College of Medicine. The section is being established this summer and will enlarge the teaching program of the College and the chemical diagnostic services to patients at John Gaston Hospital, the teaching hospital of the College.

Dr. R. R. Overman and Dr. Donald B. Zilversmit, physiologists at the University of Tennessee Medical Units, Memphis, have been awarded research grants by the American Cancer Society. Dr. Overman received $6,500 to investigate the role of two chemical elements, potassium and sodium, in normal and cancerous cells of the body. Dr. Zilversmit received $5,500 to study the role of the liver in the utilization of fats by the body.

TEXAS

A two-story building to house an institute for research on blood diseases is being constructed on Baylor Hospital grounds in Dallas. Mr. and Mrs. J. K. Wadley, Texarkana, donated more than $600,000 to establish the J. K. and Susie L. Wadley Research Institute and Blood Bank as a memorial to their grandson who died of leukemia. Dr. J. M. Hill, director of the graduate research institute and blood center of Baylor Hospital, will be director of the new blood center.

Dr. E. S. McLarty, Galveston, has been appointed health officer for Galveston County.

Dr. Cornelius Pugsley, Houston, has been appointed chief of staff of Hermann Hospital.

Dr. W. A. Senglemann, Houston, has been appointed President of the medical staff of Memorial Hospital in Houston.

Dr. E. F. Jones, Galveston, is the new President of the staff of St. Mary's Infirmary, Galveston.

Dr. W. F. Starley, Galveston, has been elected surgeon of the Galveston's Gary Ord Camp No. 7, United Spanish War Veterans.

Dr. Leo S. Duflot, Galveston, was married recently to Miss Rosemary Collins.

The Secretary of State of Texas has granted the Texas Medical Association a fifty year extension of its 1901 charter.

Dr. Henry R. Viets, Boston, Chairman of the Council on Scientific Assemblies of the American Medical Association, has been appointed lecturer in neurology and historical and cultural medicine at the University of Texas Medical Branch, Galveston. He will spend a week each semester at the University.

Dr. Ludwik Anigstein and Dr. Don W. Micks (D.Sc.), of the Department of Preventive Medicine and Public Health of the University of Texas Medical Branch, Galveston, plan a scientific expedition to the Republic of Columbia for the medical branch and the Museum of Natural History of Houston. They will collect insect vectors for tropical disease.

Dr. James Lewis Pipkin, San Antonio, has been elected Vice-President of the American Academy of Dermatology and Syphilology.

The residency program in pathology at the Veterans Administration Hospital of the Texas Medical Center, Houston, has been approved by the Council on Medical Education and Hospitals of the American Medical Association. Training includes a four-year program in pathologic anatomy and clinical pathology.

Dr. James E. Dailey, Houston, has been elected President of the Texas Chapter of the American Society of Chest Physicians.

Dr. W. Harris Connor, Houston, has been elected President of the Texas Dermatological Society.

Dr. W. M. Pratt, Houston, has been elected President of the Texas Air Medics Association.

Dr. Paul V. Ledbetter, Houston, has been elected President of the Texas Heart Association.

Continued on page 54

when "eating for two" ...plenty of citrus fruits

Most obstetricians today insist that their mothers ingest plenty of vitamin C, particularly after the first trimester[1] (8 oz. citrus juice during pregnancy, 12 oz. while lactating).[6] Pregnancy is thus made safer because toxemia is thereby reduced.[7] Also, more babies are born normally and with a higher birth weight, while premature and still births are fewer.[3,4] In addition, both maternal and infant health is improved postpartum when an adequate vitamin C regimen has been followed throughout pregnancy.[2] Most mothers enjoy the flavor of fresh Florida citrus fruits (so rich in vitamin C and containing other nutrients*), as well as the energy pick-up provided by their easily assimilable fruit sugars.[5]

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**Citrus fruits—among the richest known sources of vitamin C—also contain vitamins A and B, readily assimilable natural fruit sugars, and other factors, such as iron, calcium, citrates and citric acid.*

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References:

1. Burke, B. S. and Stuart, H. C.: J.A.M.A., 137:119, 1948. 2. Burke, B. S. et al.: Am. J. Obst. & Gynec., 46:38, 1943. 3. Burke, B. S. et al.: J. Nutrition, 26:569, 1943. 4. Javert, C. T. and Finn, W. F.: Texas State J. Med., 46:745, 1950. 5. McLester, J. S.: Nutrition and Diet in Health and Disease, Saunders, Phila., 4th ed., 1944. 6. National Research Council: "Recommended Food and Nutrition Board, Daily Allowances for Specific Nutrients," Wash., D. C., 1948. 7. People's League of Health: J. Lancet, 2:10, 1942.

FLORIDA
Oranges • Grapefruit
Tangerines

Continued from page 52

VIRGINIA

Dr. E. Barksdale, Dr. W. S. Ferguson, Dr. R. M. Taliaferro, and Dr. J. W. Walters, all of Lynchburg, have been elected to Honorary Membership in the Lynchburg Academy of Medicine.

Dr. Isa Costen Grant, Richmond, has been named chief of the Division of Maternal and Child Health in the Richmond City Health Department.

Dr. E. L. Kendig, Jr., Richmond, has been elected President of the Virginia Pediatric Society. Dr. Paul Hogg, Newport News, has been elected Vice-President, and Dr. T. J. Humphries, Roanoke, has been elected Secretary-Treasurer.

Dr. Frederick H. Yorkoff, Clintwood, has been appointed assistant chief of professional services at the Fort Myer Army Dispensary in Arlington. He has moved to Washington, D. C.

Dr. Herman A. Meyersburg, formerly of Norfolk, has accepted a position with the Mental Hygiene Clinic of the Veterans Administration Regional office in Washington, D. C. He will take further training at the Washington Psychoanalytic Institute in Washington.

The Tuberculosis Foundation of Virginia has received $200,000 from the estate of Mrs. Jennie W. Brothers of Fayetteville. The fund, to be used to care for indigent tuberculosis patients, will be known as the Pattie Mae Fund.

WEST VIRGINIA

The Eighty-Fourth Annual Meeting of the West Virginia State Medical Association will be held July 19-21 at White Sulphur Springs. Dr. John W. Cline, San Francisco, California, President of the American Medical Association, will head the list of guest speakers. The program committee for the meeting is composed of Dr. L. J. Pace, Princeton, Chairman, Dr. Cecil O. Post, Clarksburg, and Dr. James L. Wade, Parkersburg. Dr. Frank J. Holroyd, Princeton, will deliver his presidential address at an open meeting Thursday evening, July 19. The first meeting of the House of Delegates will be held Thursday afternoon, July 19, and the final meeting will be held Friday, July 20.

Dr. Eugene J. Nicgorski, Elbert, has moved to Salem, Massachusetts, where he will continue in his practice.

Dr. E. Q. Hull, Charleston, has accepted a position with the Atomic Energy Commission and has moved to North Augusta, South Carolina.

Dr. Altamont A. Bracey, Welch, has moved to South Hill, Virginia, where he will engage in the practice of traumatic surgery.

Dr. Constantine Veremakis, formerly of Wheeling, has moved to Stanford, Connecticut, where he will continue in his practice of anesthesiology.

Dr. Roy R. Summers, Charleston, Dr. Thomas B. Baer, Dr. John J. Sherman, Dr. M. L. White, Jr., and Dr. W. R. Wilkinson, Huntington, Dr. A. Kyle Bush, Phillippi, and Dr. C. B. Hughes, Jr., Montgomery, were recently awarded senior fellowships in the Southeastern Surgical Congress held at Hollywood Beach, Florida. Dr. Wade H. St. Clair, Bluefield, was elected an Honorary Fellow of the Congress.

A preconvention meeting of the Council of the West Virginia Medical Association will be held July 18 at the Greenbrier. Dr. Charles E. Watkins, Oak Hill, is Chairman.

Dr. J. L. Thompson, Weirton, has been appointed chief surgeon and director of the Medical Department of the Weirton Steel Company at Weirton. He succeeds Dr. L. A. Whitaker who will continue as consultant to the Medical Department.

Classified Advertisements

PHYSICIANS interested or trained in pediatrics or public health needed in Health Department; salary $5907 to $9207; Civil Service; Pension. Write Dr. E. R. Krumbiegel, Commissioner of Health, Milwaukee, Wisconsin.

GENERAL PRACTITIONERS STUDY CLUB INTERNATIONAL

The annual convention of the General Practitioners Study Club International will be held at Rome, Italy, September 12-15, 1951. Stratocruiser leaves New York September 1, 1951, for London, returning to New York via Lisbon on September 25th. Lectures and clinics to be held in London and Paris. All physicians, their families and friends are invited to attend.

For itinerary and reservations write to John O'Connell, M.D., 10300 Lackland Road, St. Louis 14, Missouri. Complete cost of trip is $1,295 per person.

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Orthopedics
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Radiology
Surgery
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Compare this significant data evaluating the potency of the IMPROVED germicide

SPORULATING BACTERIA	50% DRIED BLOOD	WITHOUT BLOOD
Cl. tetani	3 hours	3 hours
Cl. welchii	2 hours	2 hours
B. anthracis	1½ hours	1½ hours
VEGETATIVE BACTERIA		
Staph. aureus	5 min.	15 sec.
E. coli	3 min.	15 sec.
Strept. hemolyticus	2 min.	15 sec.

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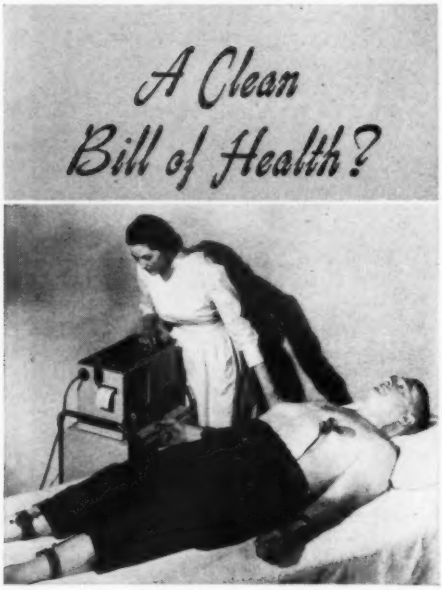

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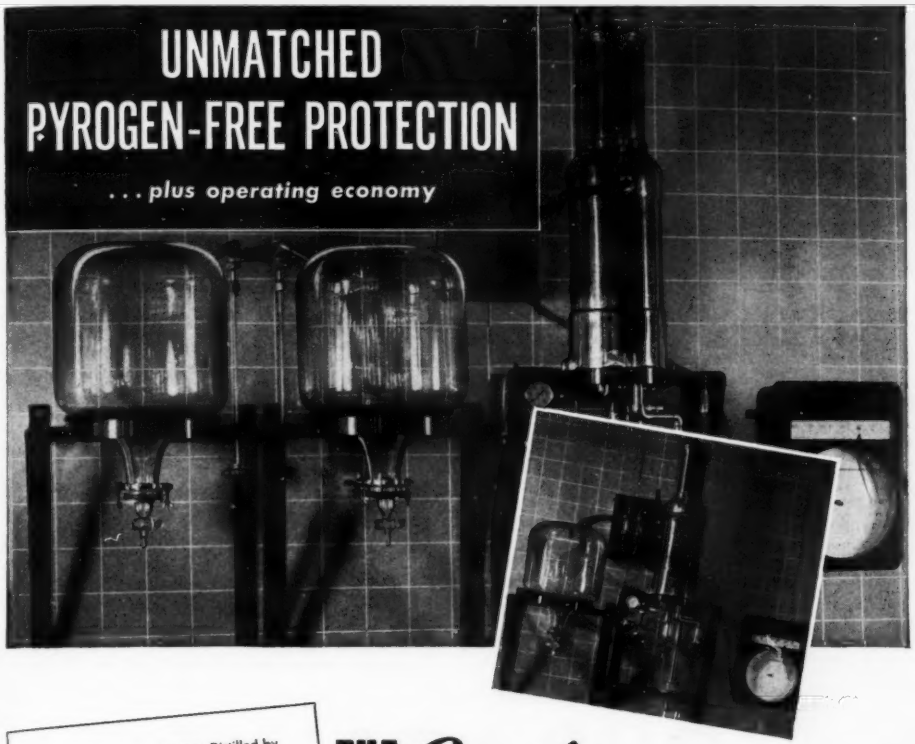

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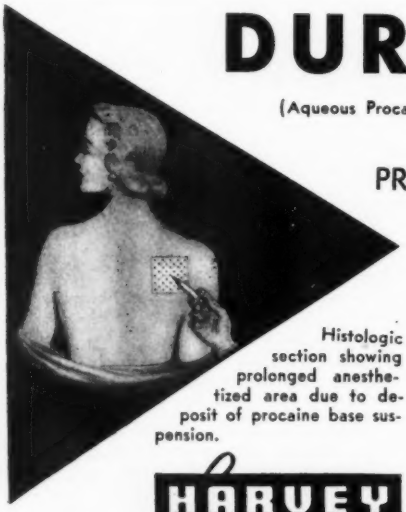

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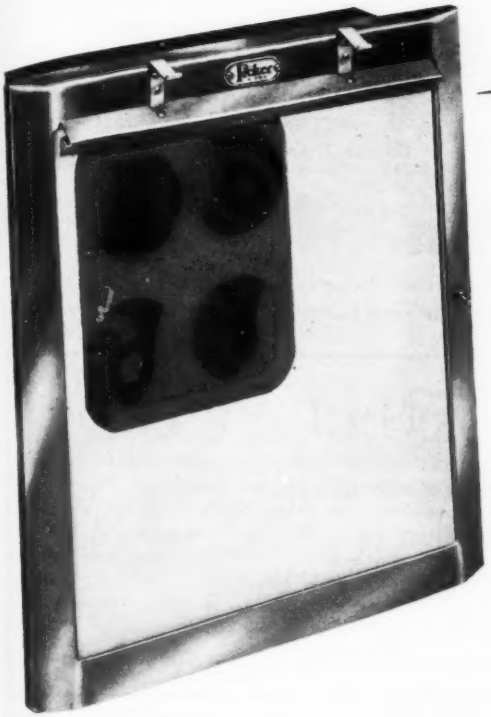

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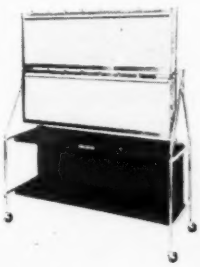
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